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Current Issues in Cancer

Genes, dreams, and cancer

Karol Sikora

This is the eighth in a series of articles examining developments in cancer and updating what we know about the disease

There have been tremendous advances in our understanding of cancer from the application of molecular biology over the past decade. The disease is caused by a series of defects in the genes that accelerate growth—oncogenes—and those that slow down cellular turnover—tumour suppressor genes. The proteins they encode provide a promising hunting ground in which to design and test new anticancer drugs. Several treatment strategies are now under clinical trial entailing direct gene transfer. These include the use of gene marking to detect minimal residual disease, the production of novel cancer vaccines by the insertion of genes which uncloak cancer cells so making them visible to the host's immune system, the isolation and coupling of cancer specific molecular switches upstream of drug activating genes, and the correction of aberrant oncogenes or tumour suppressor genes. The issues in these approaches are likely to have a profound impact on the management of cancer patients as we enter the next century.

The key problem in the effective treatment of patients with solid tumours is the similarity between tumour cells and normal cells. Local procedures such as surgery and radiotherapy may be effective, but only if the malignant cells are confined to the area treated. This is so in around one third of cancer patients. For most, some form of systemic selective therapy is required. Though many cytotoxic drugs are available, only a small proportion of patients are actually cured by them. The success stories in Hodgkin's disease, non-Hodgkin's lymphoma, childhood leukaemia, choriocarcinoma, and germ cell tumours have simply not materialised for the common cancers such as those of the lung, breast, or colon. And this is despite enormous efforts in new drug development, clinical trials of novel drug combinations, the addition of cytokines, high dose regimens, and even bone marrow rescue procedures.

Molecular biology of cancer

Against this disappointing clinical backdrop there has been a dramatic increase in information on the molecular biology of cancer. Oncogenes were first discovered in the RNA tumour viruses of chickens, cats, and rodents. Oncogenes encode a series of molecular cogs that control the growth of cells by transmitting signals from the cell surface through to the nucleus. Mutations which lead to oncogene products with increased activity or their excess production may result in abnormal growth patterns and

cancer.¹ The more recently discovered tumour suppressor genes encode proteins that act as the cell's braking system.² When these are deleted, down-regulated, or mutated abnormal growth may again be the outcome (fig 1). Probably four to six genetic changes are necessary to produce most human cancers. Though our knowledge of growth control is still rudimentary, we have at last had the first glimpse of its complexity. This has brought a new vision with which to develop novel selective mechanisms to destroy tumours.

There are many potential avenues to follow in devising future treatments. The first is to learn how the growth signalling apparatus works in detail and to develop drugs that can target specific components within it. Examples being actively pursued include the construction of growth factor analogues which can slow growth by competitively binding to receptors³ and dimerisation inhibitors to block cell surface receptor

FIG 1—Interacting pathways of oncogenes and tumour suppressor genes

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activity by preventing the aggregation of receptors—an essential process in their activation.⁴ Other targets lie within the cell and include key signalling enzymes such as tyrosine kinase and protein kinase C. In the nucleus specific transcription factors that control the expression of genes provide the ultimate tollgate for life's processes. These pathways can be interrupted.⁵ A final approach is to use molecular genetics to specifically manipulate tumour cells resulting in their destruction—a technique popularly called gene therapy.⁶

Getting genes into cells

There are many methods for getting foreign genes into cells so that their DNA can be transcribed into mRNA and the encoded protein product synthesised. Physical methods such as direct microinjection, electroporation, calcium phosphate transfection, liposomal encapsulation, and dextran precipitation are well established in the laboratory.⁷ Unfortunately, these methods are inefficient in getting stable DNA incorporation and cannot readily be adapted for wide in vivo use. Viral methods are much more effective. The virus is altered to contain the gene of interest and its normal infective machinery used to carry this into cells. Retroviral delivery systems are the best developed.⁸ But there are many problems—the lack of tissue tropism, their rapid inactivation by antibodies when given systemically, their small size which limits their carrying capacity, and their inability to infect non-replicating cells. Adenoviruses, adenoassociated herpes simplex virus, and other, larger viruses that exhibit tissue specific tropism are now under investigation as vectors for potential therapeutic use.⁹

The main problem for the cancer gene therapist is how to get new genes into every tumour cell. If this cannot be achieved, then any malignant cells that remain unaffected will emerge as a resistant clone. Though we do not have the ideal vectors as yet, the considerable research endeavour on this topic will almost certainly produce novel agents for gene transfer.

Gene therapy

The pace of the acquisition of molecular knowledge is accelerating. It is likely that the human genome will be sequenced before the end of this decade, bringing with it many potential benefits as well as ethical dilemmas.¹⁰ We may even see the emergence of a genetic underclass—unable to get insurance, employment, and possibly even to get married because of unfavourable DNA sequences.¹¹ The process of gene transcription will soon be understood so that we can effectively control the selective expression of DNA. The widespread application of gene therapy technology to many diseases is already breaking down the traditional boundaries into which modern high technology medicine has been split.¹² The drive to develop novel vector systems and techniques to knock out specific genes and to selectively control transcription applies equally to cardiology, nephrology, and paediatrics as well as to oncology. For this reason many of the problems that currently appear insurmountable are likely to be solved. There are already over 100 protocols accepted or under consideration by various ethical committees for gene therapy trials worldwide—the majority in the United States. Most are for cancer, in which the ethics are perhaps simplest, with the lowest risk-benefit ratio. Six strategies are currently under investigation.

GENETIC TAGGING

There are several settings in which using a genetic marker to tag tumour cells may help in making decisions on the optimal treatment for an individual

FIG 2—Three methods of enhancing immune recognition of tumour cells

patient. Inserting a foreign marker gene into a tumour biopsy sample and replacing the marked cells into the patient before treatment can provide a sensitive new indicator of minimal residual disease after chemotherapy. The commonest marker is the gene for neomycin phosphotransferase—the neoR gene—an enzyme which metabolises the aminoglycoside antibiotic G418.¹³ This gene, when inserted into an appropriate retroviral vector, can be stably incorporated into the host cell's genome. Originally detected by antibiotic resistance, it can now be picked up by the much more sensitive technique of polymerase chain reaction. In this way, one tumour cell among 10 million normal cells can be identified. This procedure can help in the design of aggressive chemotherapy protocols.

A particularly elegant use of this strategy has been in analysing the reasons for failure in autologous bone marrow transplantation for childhood acute myeloblastic leukaemia. Failure may be due to inadequate chemotherapy or to reinfusion of viable tumour cells in the stored marrow. Reinfused marrow was labelled with neoR and recurrent tumour analysed for the presence of this gene. In most cases tumour cells contained the marker, indicating failure of the purging process.¹⁴ Similar studies are in progress for neuroblastoma as well as chronic myeloid and acute lymphoid leukaemia.

ENHANCING TUMOUR IMMUNOGENICITY

The presence of an immune response to cancer cells has been recognised for years.¹⁵ The problem is that

human tumours seem to be predominantly weakly immunogenic. If ways could be found to elicit a more powerful immune stimulus, then effective immunotherapy could become a reality. Several observations from murine tumours indicate that one reason for weak immunogenicity of certain tumours is the failure to elicit a T helper cell response.¹⁶ This in turn releases the necessary cytokines to stimulate the production of cytolytic T cells which can destroy tumours. The expression of cytokine genes such as interleukin 2, tumour necrosis factor, and interferon in tumour cells has been shown to bypass the need for T helper cells in mice.¹⁷ Similar clinical experiments are now in progress (fig 2). Melanoma cells have been prepared from biopsy specimens and infected with a retrovirus containing the interleukin 2 gene. These cells are being used as a vaccine to elicit a more powerful immune response.

Many tumours express small amounts of the products of the major histocompatibility complex.¹⁸ These molecules are necessary for antigen presentation and their absence may help tumours evade immune scrutiny. There are now several examples of mouse model systems in which tumour cells transfected with

Box 1—Cloned genes and their promoters that may be isolated and coupled to drug activating genes for selective expression in either tumours or non-essential tissues

Selective gene	Tumour
Carcinoembryonic antigen	Colorectal cancer, other epithelial tumours
α Fetoprotein	Hepatoma, germ cell tumours
Neurone specific enolase	Small cell lung cancer
Prostate specific antigen	Prostate cancer
Thyroglobulin	Thyroid carcinoma
Tyrosinase	Melanoma
Polymorphic epithelial mucin	Breast cancer
c-erbB2	Breast and gastrointestinal cancer
c-erbB3	Breast cancer
c-erbB4	Breast and gastric cancer

major histocompatibility complex class II genes can be used not only to prevent tumour spread when given as a prophylactic vaccine but also to induce remission of established leukaemias, lymphomas, carcinomas, and sarcomas.¹⁹ Clinical experiments entailing the direct intratumoral injection of foreign HLA genes are currently in progress for several tumour types.

VECTORIZING CYTOKINES TO TUMOURS

Cytokines such as the interferons and interleukins have been actively explored for their tumoricidal properties.²⁰ Though there is evidence of cytotoxicity, their side effects are profound. Hence the dose that can safely be given is limited. It is possible to insert cytokine genes into cells that can potentially home on tumours, so releasing a high concentration of their protein product locally. Tumour necrosis factor genes have been inserted into tumour infiltrating lymphocytes from patients with melanoma and given systemically.²¹ These experiments are controversial for two reasons. Firstly, *in vitro* studies suggest that the amount of tumour necrosis factor expressed from such cells is unlikely to be enough to cause a meaningful cytotoxic effect and, secondly, inserting a foreign gene limits the ability of the lymphocyte to target into tumour masses.²² Over 15 patients have so far been treated at the National Cancer Institute in the United States and the results are eagerly awaited.

INSERTING DRUG ACTIVATING GENES

The main problem with existing chemotherapy is its lack of selectivity. If drug activating genes could be inserted which would be expressed only in cancer cells, then giving an appropriate prodrug could be highly selective.²³ There are now many examples of genes preferentially expressed in tumours. In some cases their promoters have been isolated and coupled to drug activating enzymes.²⁴ Examples include α fetoprotein in hepatoma, tyrosinase in melanoma, prostate specific antigen in prostate cancer, and c-erbB2 in breast cancer (box 1). These promoters can be coupled to enzymes such as cytosine deaminase or thymidine kinase, so producing unique retroviral vectors which can infect all cells but can be expressed only in tumour cells (fig 3). These suicide or Trojan horse vectors may not have absolute tumour specificity, but this may not be essential; it may be possible to perform a genetic prostatectomy or mastectomy, so effectively destroying all tumour cells.

Much work is currently in progress to develop both the promoter systems, which rely on differential transcription control, and also the design of the drug activating systems. Cytosine deaminase, for example, converts the comparatively non-toxic antifungal drug flucytosine to the cytotoxic fluorouracil. Both drugs

FIG 3—"Trojan horse" vector system

Many breast cancer cells express high levels of c-erbB2 oncogene product. Vector consists of retrovirus in which pol and env genes have been replaced. Virus is therefore unable to replicate outside packaging cell line. Cytosine deaminase gene is driven by c-erbB2 promoter and therefore is transcribed only in tumour cells. Neo R gene is linked to SV40 promoter and therefore is switched on in both normal and malignant cells. Non-toxic flucytosine is converted to cytotoxic fluorouracil only in high c-erbB2 expressing cells, which then die releasing their cytotoxic contents which can kill neighbouring cells. Selective destruction system for tumour cells is therefore possible

Box 2—Potential risks of gene therapy

- Insertional mutagenesis leading to cancer
- Recombination of disabled vector resulting in environmental pollution by infectious recombinant virus
- Toxic shock caused by viraemia
- Transfer of non-viral exogenous genetic material
- Contamination with other deleterious viruses or organisms

are already in clinical use and provide a useful system for further development.²⁵ Other drug activating systems are being explored which release even more potent toxins. An example is the enzyme linamarase, which converts amygdalin to cyanide. Clinical trials with genetically activated prodrugs are anticipated shortly in hepatoma and pancreatic and breast cancer.

SUPPRESSING ONCOGENE EXPRESSION

Downregulation of abnormal oncogene expression has been shown to revert the malignant phenotype in various in vitro tumour lines.²⁶ It is possible to develop in vivo systems such as the insertion of genes encoding for complementary (antisense) mRNA to that produced by the oncogene. Such antigens specifically switch off the production of the abnormal protein product. The mutant form of the c-ras oncogene is an obvious target for this approach. Up to three quarters of human pancreatic cancers contain a mutation in the 12th amino acid of this protein and reversion of this change in cell lines will lead to the restoration of normal growth control.²⁷

Clearly the main problem is to ensure that every single tumour cell gets infected by the therapeutic antigen. Any cell which escapes will have a survival advantage and produce a clone of resistant tumour cells. For this reason it may be that future treatment schedules will require the repetitive administration of vectors in a similar way to fractionated radiotherapy or chemotherapy.

REPLACING DEFECTIVE TUMOUR SUPPRESSOR GENES

In cell culture malignant properties can often be reversed by inserting normal tumour suppressor genes such as retinoblastoma (RB-1), wild type p53 (Wtp53), and deleted in colorectal carcinoma (DCC).²⁸ Though tumour suppressor genes were often identified in rare tumour types, abnormalities in their expression and function are abundant in common human cancers.²⁹ As with antigen therapy, the difficulty in

this approach lies in delivering actively expressed vectors to every single tumour cell in vivo. Nevertheless, clinical experiments are in progress in non-small cell lung cancer in which retroviruses which express Wtp53 genes are being given during bronchoscopy.³⁰ No clinical results are as yet reported.

Ethics and safety

Perhaps the biggest risk from gene manipulation in vivo is the possibility of insertional mutagenesis and the activation of oncogenes leading to neoplasia (box 2).³¹ Such risks are clearly important when considering the ethical basis of gene therapy for disorders such as cystic fibrosis, haemophilia, and the haemoglobinopathies.

For patients with metastatic cancer the risks are low. Such patients are often desperate for positive results and are already searching for the gene therapy programmes described in the media. Treatments with even minimal potential benefit will be avidly considered.³² In this setting the biggest problem is offering false hope. It is unrealistic to expect such new strategies to be effective immediately. The first patients entering trials are providing much information for little personal benefit. This must be recognised by both the investigator and the patient to reduce the "breakthrough" mentality that surrounds novel cancer treatments. In the United Kingdom the Department of Health has established a central supervisory body—the Genetic Therapy Advisory Committee (GTAC)—to consider all gene therapy protocols alongside the discussions of local ethical review committees.³³

Conclusion

There have been remarkable advances in our understanding of the molecular biology of cancer. Interventional genetics is now poised to provide new selective tumour destruction mechanisms for patients with widespread cancer. The Recombinant DNA Advisory Committee (RAC) in Washington has approved over 50 protocols incorporating gene therapy for cancer. In the United Kingdom protocols are now written for seven trials which will be opening soon (box 3). There are many hurdles to overcome: how to transfer genes efficiently and stably into tumour cells in vivo; how to ensure safety for both patients and staff; and how best to place genetic approaches alongside more familiar treatments. We are witnessing the beginnings of molecular therapy.

Fifty years ago the first alkylating agents were discovered and were about to enter clinical trial as systemic chemotherapy. None of our predecessors could have predicted the successes and disappointments that have led to the practice of modern medical oncology. We are now leaving an era of empiricism and entering an age where our knowledge of genetics and logical molecular design is likely radically to change the future face of cancer treatment. Today's dreams are likely to become tomorrow's reality.

I thank Jonathan Harris, Helen Hurst, and Nicholas Lemoine for helpful discussion.

Box 3—Proposed cancer gene therapy trials in United Kingdom

● Interleukin 2—melanoma vaccine	Institute of Cancer Research, Royal Marsden, London ³⁴
● Interleukin 2—melanoma vaccine	Cancer Research Campaign, St George's, London ³⁵
● HLA-B7—bladder cancer vaccine	Imperial Cancer Research Fund, Royal London, London ³⁶
● Idiotype naked DNA—non-Hodgkin's lymphoma	Medical Research Council, Addenbrooke's, Cambridge ³⁷
● Prostate specific antigen naked DNA—prostate cancer	Imperial Cancer Research Fund, Hammersmith, London [*]
● B7.1-interleukin 2—ovarian cancer vaccine	King's College, London†
● Tyrosinase—melanoma	Imperial Cancer Research Fund, St Thomas's and Oxford ³⁸
● c-erbB2—breast cancer	Imperial Cancer Research Fund, Hammersmith, London ³⁹
● c-erbB2—cancer of pancreas	Imperial Cancer Research Fund, Hammersmith, London ⁴⁰

*A Epenetos, J Waxman, personal communication.

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Health Profile

Challenging doctors: an interview with England's chief medical officer

Richard Smith

"Part of my agenda is to ensure that professionals take the lead."

Professor Ken Calman, the chief medical officer in England, is said by many "to have a brain the size of a planet." Before taking up his present post—in 1991—he was professor of clinical oncology in Glasgow, dean of postgraduate medicine in the west of Scotland, and chief medical officer in Scotland.

rs: Many people think that the CMO doesn't have anything like the influence that he had back in the days of, for example, Sir George Godber, who was chief medical officer from 1960 to 1973. Is this true?

kc: You must look at this historically. Each CMO has found a particular niche at a particular time. George Godber was CMO in the 1960s, a time of expansion. John Simon was CMO in the 1850s and concentrated on public health issues. George Newman in the 1920s tackled—remarkably—general education, physical education, and medical education. Wilson Jamieson in the 1940s concentrated on the new NHS and setting up the World Health Organisation.

I am faced with a particular range of issues in a climate that has changed considerably since the 1960s, and my job is to look at the opportunities and see what I can do with them—to improve the health of the people and ensure that doctors are enabled to perform to the highest possible standards.

rs: So on particular subjects you might have as much influence as they had?

kc: Of course. Let me just give you three examples. The CMO—and by the CMO I mean myself and my team—remains very much the leader in shaping medical education; the *Health of the Nation*; and outcomes, effectiveness, and audit. And what could be more important than these?

rs: What is the relationship between the CMO and the deputy CMO, who is the medical director of the NHS

Executive? And what is the relationship between the Department of Health and the executive? People are confused.

kc: I think it's straightforward. There is a Department of Health, and within the department there is the NHS Executive. The permanent secretary, the CMO, and the chief executive of the NHS Executive form the top of the office team and work closely together. The CMO has two deputies—one who works with wider health policy and one who works primarily with the NHS, although there's a lot of come and go between them. The relationship between the medical director of the NHS Executive and the CMO is a very close one, and we switch around depending on the key issues. Medical education is a topic that interests me particularly, and I've generally taken a lead on that. The medical director of the NHS Executive has an interest in many other things, for which he is very much in the lead. It's a team effort, and it's important that it's seen like that.

rs: So the relationship could work in another way with two different individuals?

kc: Several years ago there were four deputy chief medical officers, as well as some other grade 2 doctors. Now there are only two DCMOs. We have to share the load and be flexible to work effectively.

Power remains in the hands of doctors

rs: Although you may feel that you still have considerable influence within the Department of Health, I think that doctors generally feel that they don't have the influence that they once had. Is that true? Does it matter?

kc: It certainly matters that they continue to have influence, and influence relates to leadership. I think

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