COMMENTARY

Tumour antigens on tap

See page 295

Harnessing the power of the immune system to fight tumours has been a long-standing goal of cancer researchers. The immune system is a perfect complement to current therapies in that it is highly specific, can distinguish cancer cells from healthy tissue, and can deal with disseminated cancer at a cellular level. The hope is that by adding immunotherapy to the currently available portfolio of anticancer therapies, clinical outcomes will improve exponentially.

For a long time the availability of tumour antigens has been the major limitation to effective and widely applicable immunotherapy. Until the identification of melanoma antigens in the early 1990s, no human tumour antigens had been defined molecularly, and even their existence had been repeatedly questioned. The list of documented tumour antigens has grown considerably since then and now includes antigens expressed on a range of adenocarcinomas and tumours of the lymphohaemopoietic system.¹

Defining tumour antigens at the molecular level is insufficient to translate into useful therapies. T lymphocytes, the principal anti-tumour effector cells, only recognise tumour antigens in association with the hugely polymorphic HLA molecules in the host. Therefore, antigens that are potentially effective in patients expressing one HLA allele may be weak or ineffective in patients expressing a different HLA molecule. In addition, there are grounds for caution in advocating immunotherapies that are directed against single tumour antigens. Tumours may lose or downregulate expression of those antigens against which immunotherapy has been targeted, resulting in the selection of resistant clones. Both of the above limitations are addressed by using vaccines that include the widest possible range of antigens. For many investigators, fresh autologous tumour has been the logical source.

The question then becomes: how much tumour can be realistically obtained from patients to generate a sufficient amount of vaccine? Investigators have used various sources: bulk surgical samples are a useful but limited source and may often contain healthy tissue which will, at the least, dilute the strength of the useful tumour antigens. Some tumours cells can be cultured; however, this may result in drifts in the antigenic make-up of the cells compared with their primary source. Lastly, the more sophisticated the manipulations to isolate autologous tumour antigens become, the fewer are the medical centres able to offer this choice to patients.

This is where the study by Fabrice Andre and colleagues, in today's issue of *The Lancet*, offers a fresh approach to tumour-antigen isolation. The investigators have previously reported on the existence of exosomes, subcellular particles of 60–90 nm diameter that are released by cultured cells and carry various transmembrane molecules, MHC molecules, and, when tumour-derived, tumour antigens.^{2–4} They have also shown that exosomes are more effective than tumour-cell lysates at loading antigen-presenting cells such as dendritic cells in vitro.⁴ In today's report,

Andre and colleagues show that exosomes can also be obtained in large quantity from peritoneal fluid of patients with malignant effusions. Such exosomes are tumour-derived, because they contain Mart1/MelanA in two patients with melanoma or Her2/Neu in patients with ovarian or breast cancer, can be used to restimulate established anti-tumour T-cell lines in vitro, and induce the activation of patient-derived T cells to autologous tumour antigens. Everything seems to be set for the next step, where exosomes will be used in vaccines or perhaps to generate large numbers of tumour-specific T cells for adoptive immunotherapy.

Some questions remain. Will exosomes solve the problems of tumour-antigen supply for clinical application? Can exosomes be obtained from most patients, or only from those with a large tumour-load? Will it be feasible to create exosome banks, using the peritoneal cavities of donor animals, to generate tumour-antigen sources to allow for the treatment of patients with less advanced disease? Do exosomes have any regulatory role in the immune response? These questions aside, the potential of this discovery rests not only with the possible clinical applicability of exosomes, but also as a means for rapid identification of tumour antigens and as a novel way to generate anti-tumour immune responses in vivo and in vitro.

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Risk of cancer after growth-hormone treatment

See page 273

In this issue of *The Lancet*, Anthony Swerdlow and colleagues report findings on cancer risk in a cohort of 1848 patients who were deficient in growth hormone and treated with human-pituitary growth hormone at young ages between 1959 and 1985. These individuals were followed up for cancer incidence to December, 1995, and for mortality to December, 2000. Compared with cancer rates in the general population, rates in treated patients showed significantly increased risks of mortality from cancer overall, particularly from colorectal cancer and Hodgkin's disease.

The investigators are rightly cautious in their interpretations of the findings. Several points, mostly

discussed by the investigators, are worth emphasising. Most importantly, the cases are few in number. It would be unwise to draw firm conclusions from two cases of colorectal cancer, even though only 0·25 were expected in such a young population and even though the results are statistically significant. Because of the small numbers, the confidence intervals for colon cancer mortality include relative rates that range from 1·3-fold to more than 30-fold increases over control. Most of the patients followed up were under the age of 45. The incidence of most cancers increases logarithmically with age, and the individuals in the cohort are just beginning to enter the age groups when cancer incidence starts to rise precipitously. Continued follow-up of these individuals is imperative, as there are precedents for exposures at critical periods early in life that can influence life-long cancer risk.¹

Although the latest findings are not definitive, they are provocative and somewhat worrisome. Moreover, the results are consistent with an increasing body of literature which suggests that patients with acromegaly,² adults with circulating concentrations of insulin-like growth factor I (IGF-I) at the high end of the normal range,³⁻⁹ and taller individuals^{10,11} are at increased risk of epithelial cancers, especially colorectal cancers.^{2,4,6-8} Of particular interest in this context is a recent report that a common polymorphism in the human growth-hormone gene that is associated with reduced concentrations of growth hormone and IGF-I is inversely associated with colorectal cancer risk.¹²

The results could have major implications because more than 100 000 patients worldwide are estimated to have received growth-hormone treatments.¹³ This figure may be a conservative estimate in view of the increasing use of growth hormone for various off-label indications. However, the relevance of the findings to current therapy with recombinant growth hormone is unclear. In the cohort studied by Swerdlow and colleagues, the preparations and doses of growth hormone were not equivalent to current therapy with recombinant growth hormone, and were given two or three times per week. Recombinant growth hormone is typically given daily at lower doses.

Any increased cancer risk in people treated with growth hormone is plausibly related to the effects of treatments on concentrations of IGF-I and IGF-binding proteins. It was not possible to compare these concentrations in the population studied with those achieved with more modern replacement regimens for growth hormone. Nevertheless, the results do provide indirect support for the view that the dosage of growth hormone used in the treatment of growth hormone deficiency should be individualised, with a target of achieving IGF-I concentrations in the normal range for the age of the patient.^{14,15} This view contrasts with more casual approaches to dosage, such as titrating dose against growth rate, or choosing an arbitrary dose based on the patient's age or weight.

It must be emphasised that the treatment of growth hormone deficiency has established health benefits, and that there is no evidence that physiological growth-hormone replacement increases cancer risk.¹³ While the data reported by Swerdlow and colleagues should not discourage appropriate treatment of growth hormone deficiency, they should provoke reassessment of the risks and benefits of growth hormone therapy for more controversial indications that are unrelated to growth hormone deficiency, particularly if such treatment is prescribed for long periods. One example of potential concern is the long-term use of growth hormone administration as an "anti-ageing" regimen in healthy

middle-aged individuals who show the expected decline of circulating IGF-I concentration with age. After a 6-month study that suggested benefits for such therapy,¹⁶ the use of growth hormone has increased substantially, but the potential long-term hazards of maintaining peripubertal concentrations of IGF-I for decades have not been studied in detail. Although further research is required to find definitive answers, sufficient suggestive data exist to warrant caution rather than a cavalier attitude in the use of growth hormone. Furthermore, several pharmacological strategies^{17,18} are available to target growth hormone, and, conceivably, future data may provide a basis for investigation of the possibility that reduction of IGF-I concentrations from the high to the low end of the normal range may reduce cancer risk for certain individuals.

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