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The case for cancer immunotherapy

Traditional modalities for the treatment of patients with cancer have consisted of surgery, chemotherapy and radiation therapy, but immunotherapy has recently emerged as an innovative tool in the fight against malignancies [1]. Immunotherapy can be divided into two categories: active and passive. Active immunotherapy, aims mainly to elicit the body's own response to attack the tumor cells, whereas passive immunotherapy relies on therapeutics that can directly mediate the killing of the tumor. Examples of active immunotherapeutic agents include cytokines and cancer vaccines, whereas targeting antibodies and adoptive transfer of tumor-specific T lymphocytes are components of passive immunotherapy. These were summarized and discussed, alongside other novel approaches in the field, by Whelan *et al.* in a recent article in *Drug Discovery Today* [2].

So, does immunotherapy work in the treatment of patients with cancer? The answer is absolutely yes. For example, although interleukin-2 (IL-2) is not intrinsically cytotoxic to tumor cells *in vitro*, it can lead to dramatic tumor regression in patients with metastatic melanoma or renal cell cancer. Moreover, most patients who show a complete tumor response to IL-2 remain disease-free during long-term follow-up [3]. Similarly, targeting antibodies have become integral therapies in the treatment of patients with breast cancer and B-cell malignancies [4,5]. More recently, a peptide vaccine and an adoptive transfer of tumor-reactive T cells have independently led to dramatic responses in patients with metastatic melanoma [6,7].

How can we further these successes? Several areas might warrant intensive research. First, cancer vaccines might potentially be effective, as described. However, choosing candidate vaccine(s) from the ever-growing list of tumor or tumor-associated antigens that have been identified appears to be a daunting task. The most promising antigens or epitopes might be ones that are expressed on the surface of tumor cells and/or that can elicit cytotoxic T lymphocytes (CTLs) reactive to tumors. It might also be desirable to include both major histocompatibility complex (MHC) class I and class II epitopes in cancer vaccines, because there is clear evidence that $CD4^+$ cells can help the clonal expansion of CTLs. The use of vectors expressing multiple epitopes, whole antigenic proteins, or infusion of antigen-presenting cells (APCs) modified by such vectors, would help to accomplish these goals.

Second, we expect to see more antibodies developed to target tumor or tumor-associated antigens, especially for hematological malignancies. Modification of these antibodies, such as conjugation with toxins to enhance their efficacy, will become increasingly common [8,9]. Third, several advantages of adoptive transfer of anti-tumor T lymphocytes make it a promising approach in the treatment of patients with cancer. *Ex vivo* activation and culturing of these anti-tumor T cells could remove the inhibitory effects that the tumor environment might have imposed on them *in vivo*. In addition, recent advances in genetic modification of T cells could expand their functional repertoire in patients [10]. Furthermore, the adoptive transfer approach might be applicable to other cancers as more T cells reactive to particular tumor or tumor-associated antigens become available.

Although immunotherapy is not available to every oncologist who treats cancer patients, it should prove to be an essential armamentarium in our quest for a cure for cancer.

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Challenges in molecular analysis for individualized cancer therapy

Chemotherapy is an important component of cancer treatment regimes, but cure rates are constrained not only by the limited range of agents currently available and their adverse side effects, but also by variations in individual responses. This variation might be due to individual host factors, such as drug metabolism and clearance, or to resistance (inherent or acquired) of the tumour cells to drugs [1]. Laboratory tests that could predict individual tumour sensitivity or resistance to chemotherapy would be valuable, and would allow optimal choice of therapeutic agents and/or circumvention therapy (although options in both are still somewhat limited). In a recent article in Drug Discovery Today [2], Huang and Sadée review developments in the use of DNA microarrays for prediction of individual sensitivity and for identification of gene expression sets relevant to chemoresponsiveness in cancer patients.

Theoretically at least, DNA microarrays should allow the assessment of resistance-associated genome-wide mRNA expression patterns, which should in turn permit the design of smaller arrays for more economic routine use. However, the data available so far are insufficient for routine application. Practical difficulties will include tumour progression over time and differences in gene expression between primary tumours and metastases; we still do not know the proportion of cases in which surgical or biopsy material (even pure tumour tissue obtained from laser capture microdissection) will predict the overall behaviour of a tumour over the course of the treatment cycle.

The analysis of tumour-derived proteins in blood has its own set of technical and interpretational problems, but has the attraction of allowing repeated sampling and monitoring of response to treatment; recent technical advances might make this approach more feasible [3,4]. Somewhat surprisingly, well-controlled studies have shown the presence in serum of tumour-derived mRNA for some genes [5]; the possible diagnostic potential of these findings is not yet clear. It should also be remembered that resistance to therapy might relate to physical factors, such as poor vascularization and associated poor supply of drug and oxygen, and it is not clear to what extent microarrays and related techniques might detect such mechanisms. The current range of therapeutic responses to such diagnoses is also unclear. Indeed, in spite of the impressive technical advances in 'chemogenomics', the collection of agents effective against, for example, cancers of the lung, colon, brain and prostate is small. The therapeutic options for dealing with multidrug-resistant tumours, whether resistance is inherent or acquired, are also severely limited. The immediate benefits arising from DNA microarray and proteomic analysis of tumours could, therefore, involve identification of new targets and elucidation of the molecular mechanisms of drug resistance, invasiveness and other treatment-relevant properties [6]. Application in individualized therapy might have to await exploitation of such mechanism/target identification in the discovery of new therapeutics and circumvention strategies.

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