Leading article

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Immunotherapy for cancer

The last decade has witnessed a phenomenal increase in technological developments in the biological sciences. These include such procedures as somatic cell hybridization for the production of murine and human monoclonal antibodies, recombinant technology for the production of growth factors which were otherwise unobtainable in large quantities by cell culture techniques, and retroviral gene transfer for the genetic modification of cells[1]. These and other procedures have facilitated the development of contemporary immunotherapy for certain types of malignant disease.

For the classical immunologist the generation of endogenous tumour-specific immune responses was unthinkable in the absence of any convincing evidence for the existence of tumour-specific antigens. However, there is now overwhelming evidence for the presence of such antigens on at least one human tumour, malignant melanoma, against which autologous tumour-specific cytotoxic T lymphocytes have been identified in most patients[2]. These specific tumour-infiltrating lymphocytes (TIL) lyse the patient's own tumour cells in a major histocompatibility complex (MHC)-restricted fashion and do so with approximately 100 times the efficacy of peripheral blood lymphocytes (lymphokine-activated killer (LAK) cells) activated non-specifically with the T cell growth factor interleukin 2 (IL-2). Furthermore, when these activated TIL cells are expanded with IL-2 and transferred back adoptively into the patient, they specifically 'home' into tumour sites[3] and, in combination with IL-2 infusion, have been reported to cause tumour regression in 50 per cent of patients so treated[4]. Current experiments are in progress to modify these TIL cells genetically, arming them with activated genes for cytotoxic cytokines, such as tumour necrosis factor (TNF), so that when they home into secondary tumour sites, they release the cytokines and bring about oncolysis[5].

Adoptive cellular immunotherapy with *in vitro* activated LAK or TIL cells is, at present, highly labour-intensive and requires skills which are not universally available. Whether or not treatment with genetically modified TIL cells will be successful remains to be seen, but the concept of tailoring individual therapy for particular patients is an attractive one. However, in practical terms it is likely that immunotherapy will only really be accepted if it can be taken 'off the shelf' and administered without the necessity for the complexities and potential hazards of *ex vivo* lymphocyte manipulation.

Nevertheless, current results provide a forcible argument that for advanced malignant melanoma and hypernephroma IL-2-based treatments, perhaps in combination with recombinant interferons, provide the highest tumour response rates and are associated with prolonged survival[6]. The cost of such treatments, both financial and in terms of toxicity, has led some to question their application. However, many of the patients suffering from these otherwise untreatable diseases are young, and it seems quite unreasonable that they should be refused the opportunity of a 25 per cent chance of responding to combination therapy with IL-2 simply on the basis of cost, which is little more than that for a course of one of the newer antibiotic combinations.

Can these approaches be exploited for the treatment of other tumours? As yet the generation of tumour-specific cytotoxic T lymphocytes has not been convincingly demonstrated for the majority of common tumours. Similarly, attempts to use the patient as his or her own 'test-tube' for the generation of cytotoxic cells by administering IL-2 alone seem to be effective in only 15–25 per cent of those patients with susceptible tumours. Considerable evidence exists to suggest that this is not simply due to the failure of such tumours to express tumour-specific antigens, together with HLA-antigens, but also because of the elaboration of potently suppressive molecules by the tumours themselves, thus subverting the endogenous anti-tumour response[7,8]. Once the identity of these moieties has been ascertained, other strategies might be invoked to evade their influence. This may be of importance even in the absence of defined tumour-specific antigens since the expression of oncogene-encoded proteins may also serve both as sensitizing molecules and target structures for the generation of specific cytotoxic lymphocytes against tumours such as colorectal

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cancer. This concept is becoming a major focus of intensive research by tumour immunologists[9].

It must not be forgotten that recombinant technology has also provided us with reagents whose beneficial therapeutic effects cannot be entirely explained on an immunological basis. For example, the recent description of response rates in excess of 50 per cent in patients with advanced colorectal cancer treated with a combination of 5-fluorouracil and recombinant α_2-interferon[10] represents an important advance which is under detailed study in phase II/III trials. Similarly, cytotoxic drugs may potentiate the biological effects of recombinant cytokines and result in clinically advantageous therapeutic responses[11]. In view of recent reports, these findings may have important implications for the development of adjuvant therapy for colorectal cancer[12]. This is entirely in keeping with the concept that biological therapies are most effective in the presence of minimal residual disease.

Enthusiasm for cancer immunotherapy has waxed and waned over the past half century but has become invigorated by the 'new biology'. The present renaissance of immunotherapy promises to be durable simply because, at long last, it appears to be effective for certain types of malignancy. The challenge is to expand the frequency and the repertoire of responsive tumours.

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