

Commentary

Current problems in the development of specific immunotherapeutic approaches to cancer

Over the past decade there has been a widespread resurgence of interest in the concept of cancer immunotherapy and the design of new cancer vaccines. The discovery of tumour specific and tumour associated antigens has resulted in a large number of targets that are currently being developed as potential clinical products. These are comprehensively reviewed by Jäger *et al.*¹

Although the identification of tumour antigen epitopes by cytotoxic T lymphocytes (CTL) is certainly an elegant and logical approach, there is a disturbing lack of correlation between CTL activity to these epitopes and clinical response.² Moreover, it seems that there is a distinctive lack of help for a second signal in many reductionistic approaches because responses are often seen only after the addition of interleukin 2 (IL-2).³

In addition to specific immune responses, it may be that an appropriate innate immune response is as important or more important for cancer immunotherapy to be effective. Indeed, there are many reports of non-specific treatments, such as interlesional BCG or systemic cytokines such as interferon and IL-2, having singular activity in malignant melanoma and renal cell cancer.⁴ The role of non-specific immunomodulators appears to be crucial for the induction of antigen specific responses. An early randomised trial of a single antigen—namely, a ganglioside (GM2)—was reported by Livingstone and colleagues.⁵ Although those patients who had fully resected stage III melanoma and received the ganglioside vaccine did better than those who did not, the difference was only significant when the immune response to the vaccine was taken into consideration. The adjuvant used in this study was BCG; because a large proportion of the vaccinated patients did not make an immune response, QS21 was used as the adjuvant in a subsequent randomised trial between GM2 and high dose interferon. In this trial, the vaccine showed no benefit.⁶ Using BCG and allogeneic melanoma cell lines, Morton and colleagues saw a clear correlation between the immune response to the ganglioside and the outcome, strongly suggesting that this is a very important single tumour antigen.⁷ However, the specific isotype nature of the immune response correlated with clinical outcome, suggesting that it is the quality and not the quantity of the immune response induced to a vaccine/tumour antigen that is crucial in determining the outcome and not necessarily a single activity, such as the induction of CTL.⁷ Clinical evidence of strong antitumour antigen responses can be seen after the use of a non-specific immunomodulator, such as interferon α , strongly suggesting that primed T cells that are prevented from being effectors can occur in patients with melanoma.

The tumour-immune response interaction

Over the past few years, it has become increasingly apparent that the immune response is abnormal in most patients with tumours. Heriot and colleagues⁸ have reported that patients with even small colon cancers—for example, Dukes's A and B—have greatly reduced cell mediated

cytokine production using *in vitro* stimulation assays. These deficient responses return to normal after resection of the tumour. It is hard to explain these observations other than by the possibility that these, albeit, small tumours have an immunosuppressive effect that can be measured using peripheral mononuclear cells. The strength of this selective immune suppression strongly suggests that these tumours must escape the immune response to survive, grow, and metastasise. In this scenario, it is probable that good tumour antigen responses exist but that they are rendered ineffective by the anti-immune defences of the tumour, including the secretion of immunosuppressive cytokines, such as transforming growth factor β and IL-10, as well as the furnishing of ligands such as FasL, which induces apoptosis of primed and incoming CTL.

Immune evasion: a prerequisite for the development of many tumour types

The discovery that cell mediated or T helper type T (Th1) cytokines were significantly depressed in patients with early Dukes's A and B colorectal tumours⁸ led to the proposition that perhaps these tumours evolve in an area of local immunosuppression and that they need to mimic this environment to metastasise.⁹ There are only two physiological environments where cell mediated responses are switched off for the good of the host. The first is pregnancy and the second is wound healing. The first occurs presumably to prevent the rejection of the fetus or autoimmunity in the fetus; in the second case, switching off cell mediated responses prevents an autoimmune attack on a recently healed wound site. However, if the wound fails to heal because of chronic irritation, a prolonged suppression of local cell mediated responses will ensue. In addition to inducing cell mediated suppression, this will switch on the factors required to repair the wounds, including several growth factors and angiogenic factors, both of which may help a cancer cell develop. The fact that chronic inflammation may be the bedrock of cancer development is supported by the close association between long term chronic inflammatory bowel disease and colon cancer. Even in those tumours not thought to be associated with chronic inflammation *per se*, such as adenomas and polyposomas, inflammatory lesions are seen at the histological level. Moreover, clear and irrefutable data from several sources show that regularly taking aspirin (or other anti-inflammatory agents) at anti-inflammatory doses significantly reduces (by ~ 50%) the risk of contracting colon cancer over a two year period.¹⁰

Conclusions and summary

Although tumour specific responses are undoubtedly important, it may be more important to correct the immunological environment so that the effectiveness of the specific response is optimised. Although cytokine help and shifting to Th1 cytokine dominance is well recognised to be beneficial, other complementary treatments such as

anti-angiogenic agents and cox-2 inhibitors may play a major role in the establishment of an effective anticancer response. The current state of play with regard to clinical responses with single tumour antigen vaccines and the poor correlation with patients' immune responses mean that we still have a long way to go before developing effective immunotherapies against established disease.

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J Clin Pathol 2001 54: 675-676

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