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Tumour-Specific Immune Responses

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Specificity is at the heart of immunology and so is the distinction between self and non-self. Cancer cells develop from self, i.e., normal cells of the host, but only after the cells have accumulated numerous heritable epigenetic changes. In addition, there are mutational changes leading to tumour-specific proteins and potential antigens. Finding molecular targets exclusively expressed on cancer cells is one of the great hopes of cancer medicine. Targeting such tumour-specific molecules should eradicate cancer without systemic toxicity.

There is no question that all cancers in man and mouse that have been carefully analyzed express truly tumor-specific antigens that could be targeted [2]. The diversity of these antigens on cancer cells led Macfarlane Burnet to postulate that adaptive immunity evolved to cope with and prevent the development of primary cancers [3]. This concept of immune surveillance continues to stimulate not only research but also controversy regarding its general validity. Clearly, sporadic cancers can develop in normal immunocompetent hosts while retaining strong tumor-specific rejection antigens without evidence of immunoselection [4, 5].

Increasing numbers of tumor-specific mutant proteins have been identified, and the same tumor types may share some mutations. One prominent example is given by the review of **Sampson *et al.*** on targeting a EGFRvIII mutation that is widely expressed in malignant glioma and other neoplasms. The targeted mutant molecule is a constitutively active tyrosine-kinase that increases tumorigenicity and confers radiation and drug resistance. As a result of immune selection, the mutant receptor can undergo additional mutations to evade immune destruction while maintaining its tumor-promoting function. Predicting these variants and vaccinating against them before they occur may prevent tumor escape [6]. Other examples of certain tumor types sharing mutations are clear cell sarcomas, some of the most aggressive human cancers. Cancer type-specific translocations encode distinct fusion proteins in these sarcomas [7, 8]. It is likely that we are only beginning to realize the enormous opportunities of targeting tumor-specific molecules on cancer cells resulting from mutations shared among diverse cancers. This becomes evident by the review by **Schietinger *et al.*** that discusses the discovery of mutations in a chaperone Cosmc. These mutations in diverse human and murine cancer types result in tumour-specific glycopeptidic neo-epitopes recognized on the cancer cells by tumor-specific antibodies.

In addition to some mutations being shared by different cancers, each individual's cancer seems to have its own unique set of T cell-recognized antigens and somatic tumor-specific

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mutations and epitopes [9–13] some of which represent powerful rejection antigens [14]. In a landmark paper [15], Klein et al. showed decades ago that mice could be immunized to their own, i.e., autochthonous, cancers; eradication only occurred when the autochthonous cancer cells were used for immunization against subsequent challenge with the same tumor. Despite the power of Klein's observation, unique antigens have remained largely unexploited therapeutically because highly personalized therapy would be required. While the molecular identification of these unique antigens is probably not necessary for successful therapy, it is worthwhile to improve ways to immunologically target these antigens in patients. This is also suggested by the review of **Neller *et al.*** who show that whole cell vaccine or cell extracts yielded twice the number of patients with a beneficial clinical response than vaccines using molecularly defined antigens. Clearly, autologous dendritic cells loaded with autologous tumor antigen are attractive vaccines. As discussed by **Buckwalter and Srivastava** in their review, immunization with heat-shock-protein-peptide complexes is an alternative approach of immunizing against individually specific antigens without needing antigen identification. In my long experience of immunizing against individually specific antigens on murine tumours, viable cancer cells at a sublethal dose are usually most effective in causing robust, specific T cell immunity. Irradiated cancer cells, are usually less effective immunogens while tumor cell extracts seem to be the most difficult material for inducing specific and strong T cell responses. For therapy of cancer patients, obtaining viable cancer cells is usually still extremely problematic because of a remarkable, persistent difficulty with most primary human cancers of isolating cancer cells that can be propagated *in vitro*. Therefore the question arises whether immune responses to certain tumor-associated antigens (non-mutant, normal-self antigens) can be utilized as "adjuvant" to make patient's immune system "aware" of other antigens on their cancer cells including the individually specific mutant tumor antigens. In their comprehensive review, **Coulie and Lucas** discuss interesting data supporting this attractive idea.

All of the reviews in this Issue argue that clinically significant advances with immunotherapy are most likely first to occur in patients with minimal residual tumor load. However, as well known from infectious disease, active immunization in patients that are already infected rarely succeeds (except in the special case of rabies) and minimal number of cancer cells persisting in the patient may cause significant difficulties of inducing destructive immune responses. On the other hand, we have clear evidence from adoptive T cell transfer with EBV-antigen specific T cells, that large, bulky, metastatic, chemotherapy- and radiation-resistant EBV antigen-positive cancers can be eradicated in patients without side effects [16]. It would be important to develop procedures for immunizing and expanding *in vitro* patients' own lymphocytes so that they recognize the autochthonous tumor cells specifically. The induced T cells may not only be therapeutic upon reinfusion but also be used to further elucidate genetic origins of tumor-specific mutant tumor antigens. While quite effective drugs are being generated for targeting specific mutations, and while cancer treatment is getting "personal" [17], it seems ironic that individual specificity still has to conquer the field of cancer immunology although it was precisely the discovery of individually distinct tumor-specific antigens that ended the gloom over the field of cancer immunology [10, 14, 15, 18].

> "*I cannot give any scientist of any age better advice that this: The intensity of the conviction that a hypothesis is true has no bearing on whether it is true or not.* The importance of the strength of our conviction is only to provide a proportionally strong incentive to find out if the hypothesis will stand up to critical evaluation."
> Sir Peter B. Medawar Advice to a young scientist. 1979, page 39. [1]

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