Activation of lymphocyte anti-tumour responses in man: Effector heterogeneity and the search for immunomodulators

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Abstract

Data continues to accumulate on the immunological reaction against solid human cancers. The evidence at the present time supports the view that rather than being immunologically invisible, tumour cell antigens are recognised by at least three lymphocyte subsets. Helper T cells can be induced to proliferate upon exposure to cells of the autologous tumour and to secrete detectable levels of interleukin 2 (IL-2). Cultured T cell lines and clones can be shown to respond in primed lymphocyte tests not only to autologous tumour cells but also to allogeneic tumour cells of the same histology and anatomic location. Cytotoxic T cells manifest specific reactivity against cells of the autologous tumour which is distinguishable from natural killing (NK) on the basis of specificity and organ distribution. Natural killer cells can lyse freshly isolated autologous tumour cells after purification on Percoll gradients or when activated by IL-2.

There is thus a demonstrable heterogeneity of response to human cancer in unseparated lymphocyte populations and at the clonal level. In limiting dilution assays lymphocytes at the tumour site respond more frequently to autologous tumour relative to NK targets. For at least some tumours there is evidence that the expression of auto-tumour reactivity but not NK correlates with the clinical course of the disease and is a favourable prognostic indicator.

The finding of these auto-tumour reactivities has important implications for the search for immunomodulating drugs for cancer treatment. However, it must be recognised that the response is heterogenous and that the immune system comprises multiple interactive elements that exhibit both positive and negative control. Any treatment modality must take this into account and seek to focus on specific activation of the tumour lytic populations or the inhibition of negative regulatory elements as opposed to seeking a more general augmentation of immune reactivity which may, by stimulating suppressor cells, have a counterproductive effect.

Introduction

Studies of the immune response to human cancer, like many aspects of contemporary immunology, have undergone major changes in the last few years. The development of increasingly powerful techniques in cellular immunology, the advent of cell cloning and the introduction of monoclonal antibodies to identify and quantify lymphocyte subsets and classify histocompatibility antigens has allowed new insights into the nature of the host-tumour relationship. An additional important development has been the emphasis given to comparative investigations of host immune responses at the tumour site and in the peripheral circulation. These different experimental approaches have converged revealing remarkable heterogeneity in the immune response. As increasing understanding
of the controlling processes of immune reactivity has emerged through these techniques, as well as the availability of a range of regulatory molecules from molecular biology, the concept that the immune response to tumour might be manipulated to engender therapeutic benefit has moved from an empirical to a rational basis. In this review the evidence that a lymphocyte-mediated response to tumour can occur will be assessed in an attempt to answer the following questions:

1. Can human tumour evoke a cell-mediated response which is relevant to disease control?

2. What is the nature of the effector cells involved?

and

3. Does awareness of the concept of tumour antigenicity provide options for the development of new therapeutic modalities and if so what are the critical elements of a test cascade to provide evidence of efficacy?

As suggested by the title, this review will concentrate upon studies in human systems and will be directed solely towards the study of lymphocyte-mediated responses. At the present time the lymphocyte response to human cancer can be said to reside in two populations - specific T cells and natural killer cells. It is upon these two aspects that I shall concentrate in this review. The potential of cells of the monocyte-macrophage lineage to bring about tumour cell lysis is well recognised but will not be addressed here.

The heterogeneity of lymphocyte responses to cancer

The early studies of the host response to malignancy derived their rationale from the observations of tumour immunogenicity in animal tumour systems which clearly defined the existence and importance of the tumour-specific transplantation antigens in disease eradication. Subsequently, large number of studies using a variety of experimental procedures, purported to show that human tumours could indeed evoke an immunological response and the possibility of augmenting the responses for therapeutic benefit seemed high. Subsequent studies, in both spontaneously arising animal models and with human material, raised doubts about the validity of these conclusions and there arose a widely held view that tumour antigenicity is a rare phenomenon and that the immune response has little role in disease control: a view which still exists in some quarters.

The current position of those in the field of tumour immunology lies between these two extremes. While there is clear evidence of a potent surveillance system against virally induced malignancy such as that induced by Epstein Barr virus there is less conviction that the more common human tumours evoke a lymphocyte response. Nevertheless, studies continue to delineate antitumour responses using the newer techniques in immunology and the probability remains that tumours can indeed be considered a site of active immunity.

The T cell response to human cancer

Two techniques have been central to our studies of the T cell response to human cancer: the induction of proliferation of T cells in the mixed lymphocyte tumour interaction (MLTI) test and direct cytotoxicity of patients' lymphocytes against freshly isolated autologous tumour cells in short term 51Cr release assays. For both of these assays the key methodological development was procedures by which viable tumour cells freed of stromal elements and host infiltrating cells, could be recovered from the tumour sample for use either as stimulator cells or as targets in these two assays. The separation techniques have been applied principally to tumours of the lung, breast and colon and sarcoma. It was found that, in addition to tumour cells, samples