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A New Look at Tumour Immunology

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NEW DISCOVERIES clarifying the mechanism of T-cell immune recognition, together with major advances in the identification of specific genetic changes in tumours and observations on changes in the expression of HLA class I determinants on tumours, have dramatically transformed the nature of tumour immunology. It is now possible to envisage a precise understanding of the basis for immune response to tumours and so approach, in an organised way, strategies for exploiting the immune system for treatment, and even prevention, of cancers. The papers in the latest issue of Cancer Surveys [1] review the current state of knowledge and ideas concerning T-cell immune responses to tumours—ranging from the description of the basic mechanisms of immune response to review of approaches to immunotherapy and the clinical evidence for immune response to human tumours.

The most important advance in our understanding of the nature of T-cell immune recognition of cellular determinants is the demonstration that the recognised targets are processed protein antigens often intracellular, which can be represented in *in vitro* assays by short oligopeptide sequences from the relevant protein [2]. These are presented by HLA molecules on the cell surface. The structure of the HLA class I molecule, established by Bjorkman, Wiley and Strominger [3], shows where peptides are held in the cleft of the HLA molecule so that they are available for recognition by the T-cell receptor. Specific peptides, characteristically eight or nine aminoacids long, can be eluted from the HLA molecules of target cells, and this provides a totally new approach for the potential identification of T-cell target antigens [4, 5]. Particularly relevant is the finding that peptides presented by class I HLA molecules are usually derived from cytoplasmic proteins, thus the immune system can respond to internal changes in transformed cells. These advances are reviewed by McMichael, using response to influenza virus as a model. The response to virus-induced tumours is the basis for Melief and Kast's analysis of the role of peptides in T-cell recognition and the approaches that can be envisaged for peptide vaccination. The oncogenic Epstein–Barr virus (EBV), as discussed by Rickinson and colleagues, provides another valuable model for the analysis of T-cell responses and possible mechanisms of escape through mutations that lead to the loss of viral epitopes. This is, of course, only possible so long as the mutations do not at the same time lead to a loss of the transformed phenotype. Such an escape mechanism will only be effective if there is at most one or a very small number of genes controlling potentially recognisable immune targets. When this is not the case, escape must occur by mutations affecting general immune mechanisms such as the expression of HLA class I molecules or necessary accessory molecules to T-cell recognition such as LFA-3.

The first human cell line to show complete loss of surface expression of HLA–ABC was the Burkitt lymphoma-derived cell line Daudi. Early studies, which indicated that the basis for this lack of expression was lack of production of β_2-microglobulin, led to the suggestion that this reflected escape from T-cell immune response to EBV determinants during the outgrowth of the lymphoma [6]. It was then pointed out by Brodsky *et al.* (1979) that these ideas could be generalised to other tumours [7]. Thus, tumours that produced variants with lowered or altered expression, as well as of HLA-ABC or β_2-microglobulin, would be the ones against which there must have been a T-cell response to a tumour determinant. Since then, there have been many observations on human and other tumours of changes in HLA class I expression and discussions of the evidence this provides for T-cell immune attack against tumours. Kaklamanis and Hill, and Möller and Hämmerling, provide an up to date survey of data on HLA changes in tumours and the variety of mechanisms by which these can arise. Each genetic step during tumour progression must be selected for, if it is present in all, or at least a high percentage, of the cells in a tumour. Thus, if two mutational steps are needed to eliminate completely HLA–ABC expression, as is the case if this happens through recessive mutations knocking out the function of both versions of the β_2-microglobulin gene (as in the Daudi cell line), then the first mutation must itself confer at a selective advantage. This is because the probability of a first mutation, by chance, sweeping through the population of cells followed by a second mutation, even if advantageous, will be very small. It is not surprising therefore that, as shown by Smith *et al.* (1988) and others, loss of expression of single alleles is a commoner event than overall loss of expression of all HLA class I products [8]. From the point of view of escape from T-cell attack, the mutational mechanisms by which HLA expression is changed are largely irrelevant, and this is both consistent with, and can account for, the evidence for a variety of mechanisms by which these changes in expression may occur.

Möller and Hämmerling indicate that in their data there is no apparent correlation between the changes in HLA expression and tumour prognosis, although other studies have suggested that such correlations might exist. However, it is not necessarily surprising that the immune response to a tumour, signalled by a change in HLA expression, has no major effect on its outcome. Primary immune responses to specific changes in tumours may take some time to be established, by which time the tumour may be so large that outgrowth of immune resistant variants is not a limitation to the growth of the tumour, much as in the case of the development of resistance to conventional chemotherapy. This explanation is consistent with the observation, discussed by Oliver and Nouri, that in immunosuppressed transplant patients the tumours that grow out are overwhelmingly those with a viral aetiology, specifically EBV related lymphoproliferation and HPV associated skin and other cancers, and not the common carcinomas, for which there is no evidence for a viral aetiology. This is easily explained by the fact that immune response to a virus is likely to be much more readily established than that to tumour specific or associated cellular determinants, so that the immune system may play a much greater part in the prognosis of virally associated cancers than those that have no viral aetiology. This, incidentally, is a strong argument against

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the suggestion that behavioural factors may have a major influence on the incidence and prognostic outcome of cancers through their effect on immune response.

The lack of prognostic significance of immune response for the common carcinomas does not imply that immune therapy or vaccination might not be effective. It is entirely possible, given better approaches for the recognition of potential targets for T-cell attack on tumours, that stimulation of the specific immune response at a sufficiently early stage during tumour development could have therapeutic value and that vaccination against such determinants might be effective in preventing the onset of a cancer. As will increasingly be the case in future, the biological characterisation of a tumour will not so much predict prognosis but determine it through the development of therapeutic approaches targeted to particular biological properties.

Knuth *et al.* and Boon *et al.* show how it is possible to obtain cytotoxic T lymphocytes (CTLs) that are specific for tumours and how these can then be used to clone tumour specific target antigens. Boon and his colleagues have very clearly established their elegant approach to cloning using mouse model systems and tumour negative variants induced with relatively high levels of mutagens. The difference in the human situation is that the induction of human tumours is presumably not associated with high levels of mutagen, and so the problem of bystander mutations that could be targets for T-cell attack is likely to be insignificant. Boon and Knuth's groups have isolated CTLs for human melanomas and through this have cloned a melanoma specific antigen which is a considerable achievement [9]. The results suggest that potential targets may not only be novel mutations in proteins, such as in *p*53 and the *ras* oncogenes, but may also be normal genes that are abnormally expressed or expressed at higher levels as a result of the action of mutated oncogenes or transforming viruses. It seems entirely possible that changed levels of expression, such as happen as a result of *p*53 mutations, or changes in the rate of turnover of a protein could generate novel processed peptides that can be recognised by the immune system but that are not due to mutations in that protein and do not necessarily relate to a protein that is expressed only in a particular tumour. It may also be possible that the products of mutated recessive or suppressor oncogenes could be recognised as abnormal. For example, a nonsense mutation that prevents the formation of a functional product may still allow the synthesis of a partial protein product that is rapidly turned over and so enters, relatively effectively, a processing pathway creating determinants for T-cell recognition that might not be created by the normal full length functional product.

Schirrmacher and Oliver and Nouri discuss, from different angles, approaches that have been taken to vaccination against tumours in mouse models and even in humans. Schirrmacher emphasises the importance of help in the induction of primary responses and also emphasises the need for proper immunological monitoring of patients involved in any immune therapy trials. Oliver and Nouri review cases of spontaneous regression that may be considered as evidence for occasional affects of immune response on prognosis. They also discuss some of the approaches to immunotherapy using interleukin 2 (IL-2) as a non-specific stimulus of the immune system. A more promising approach, as discussed by Melief and Kast, appears to be to incorporate IL-2 or other lymphokines into autologous tumours to be used as a source of material for vaccination, after appropriate inactivation.

There seems to be little doubt that the work discussed in this issue of Cancer Surveys ultimately may lead to the development of active immunotherapy and even anti-tumour vaccination, for some specific tumours.

1. Bodmer WF, McMichael AJ. A new look at tumour immunology. *Cancer Surveys*, 1992, **13**.
2. Townsend ARM, Gotch FM, Davey J. Cytotoxic T cells recognise fragments of influenza nucleoprotein. *Cell* 1985a, **42**, 457–467.
3. Bjorkman P, Saper M, Samraoui B, Bennett W, Strominger J, Wiley D. The foreign antigen binding site and T cell recognition regions of class I histocompatibility antigens. *Nature* 1987, **329**, 512–519.
4. Falk K, Rotzschke O and Rammensee H-G. Cellular peptide composition governed by major histocompatibility complex class I molecules. *Nature* 1990, **348**, 248–251.
5. Van Bleek GM, Nathenson SM. Isolation of an endogenously processed immunodominant viral peptide from the class I H2Kb molecule. *Nature* 1990, **348**, 213.
6. Arce-Gomez B, Jones EA, Barnstaple CJ, Solomon E, Bodmer WF. The genetic control of HLA-A and B antigens in somatic cell hybrids: requirement for beta 2-microglobulin. *Tissue Antigens* 1978, **11**, 96–112.
7. Brodsky FM, Parham P, Barnstaple CJ, Crumpton MJ, Bodmer WF. Monoclonal antibodies for analysis of the HLA system. *Immunol Rev* 1979, **47**, 3–61.
8. Smith MEF, Bodmer WF, Bodmer JG. Selective loss of HLA-A,B, C locus products in colorectal adenocarcinoma. *Lancet* 1988, **i**, 823–824.
9. Van der Bruggen P, Traversari C, Chomez P, *et al.* A gene encoding an antigen recognised by cytolytic T-lymphocyte on a human melanoma. *Science* 1991, **254**, 1643–1647.