Peptide vaccination against cancer?

Micrometastases in a murine lung carcinoma model have regressed or been prevented (pages 1179–1183).

JACK L. STROMINGER

The development of our knowledge of antigen processing and presentation, and of techniques for the isolation of MHC molecules and analysis of their bound peptides, presents the opportunity to solve problems of great medical importance. These include efforts to blockade, anergize or delete T cells that mediate autoimmune diseases, as well as efforts to enhance immunity to infectious agents and tumours. A striking application to the prevention of metastatic disease in the murine Lewis lung carcinoma model is described in this issue of *Nature Medicine*[1].

The possibility of immunotherapy for human tumours is offered by the facts that some tumours (particularly melanoma and renal carcinoma) rarely undergo spontaneous remission and that low-level immune responses against some other tumours have been detected. These and other facts have led to much research aimed at identifying both tumour-specific antigens that can stimulate immune responses and the peptides from the processed antigens that are presented to the immune system by MHC molecules. In many cases, these tumour antigens are normal self-proteins with a limited cell/tissue distribution, but they may also occur in the tumour in a mutated form or be derived from virus-associated cancers. In these latter cases they would behave immunologically as foreign proteins/peptides, although self peptides can also induce immune responses.

Several genes encoding tumour antigens that may give rise to low-level immune responses in experimental animals and man have been described[2–4]. In addition, several peptide epitopes, presented by class I MHC molecules to T cells derived from tumour hosts, have been identified. These include, notably, mutant peptide(s) derived from the gap junction protein connexin-37 found in the murine Lewis lung carcinoma[5] and peptides from several different human melanoma proteins[6–9]. In addition, nine peptides from the oncogenic E6 and E7 proteins of human papilloma virus associated with cervical carcinoma that bind to HLA-A2 were identified. Four of these induced a vigorous cytoxic T-lymphocyte (CTL) response in HLA-A2 transgenic mice, and human CTL generated with these same peptides could lyse an HLA-A2 cervical carcinoma cell line[10]. Many other class I restricted peptides have also been under study[2–4]. However, in addition to class I-MHC-restricted $CD8^+$ T-cells, class II MHC-restricted $CD4^+$ T-cells can also mediate a cytolytic response[11], a fact of particular importance in the tissue destruction in some class II-associated autoimmune diseases. Notably, therefore, a peptide of 25 residues presented by a murine class II MHC protein has been identified that is associated with an immune response against a murine tumour[12].

Can such peptides be utilized in the therapy of tumours? Therapeutic goals might include prophylaxis against some tumours (vaccination), prevention of metastatic spread after surgical removal of tumours or resolution of the tumour mass itself. Several reports addressing these questions have appeared and many more studies must be in progress. For example, vaccination has protected against a tumour formed using a transformed mouse cell line[13], and established tumours in the mouse have also been eradicated using CTL raised against the same peptide[14]. Vaccination trials in humans have been initiated. Remarkably, in the present study[1], metastatic spread from a primary tumour mass that was allowed to develop for 30 days before surgical exicision and vaccination has been prevented. If these animal studies can be extended to examples of human tumours, than a window may have opened on a rational approach to the immunotherapy of at least a few human cancers.

The mode of administration of peptides is of critical importance in such trials, because soluble peptide is thought to induce tolerance (and thus may be important in the treatment of autoimmune diseases). In the present animal studies[1] which were designed to enhance immunity, peptide was administrated in incomplete Freund's adjuvant, but in human trials various other techniques may be employed. For example, peptide pulsed onto autologous antigen presenting (dendritic) cells, encapsulated in liposomes or modified as lipopeptides have all been explored. DNA vaccination simultaneous use of cytokines that may enhance immunogenicity and the linkage of CTL epitopes to helper T-cell epitopes are among other factors that must be considered. Finally, despite all efforts, tumour escape variants may constitute a major problem. Generalized loss of expression of MHC antigens or allele-specific loss are thought to represent major problems in the immune surveillance of tumours. The road ahead is unpaved and full of potholes, but the journey could be rewarding.

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Department of Molecular and Cellular Biology
Harvard University
Cambridge, Massachusetts 02138, USA
and the Dana Farber Cancer Institute
Harvard Medical School
Boston, Massachusetts 02115, USA