Cytotoxins and Cancer Immunotherapy: The Dance of the Macabre?

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The combined mortality rate for patients with breast or colorectal cancer in the United States approaches 100,000 individuals annually or approximately 270 individuals every day (1). This astounding mortality rate needs to be rapidly and positively addressed through multiple complementary efforts that must include the development of more specific, more effective, and less toxic therapeutic strategies. The present management of patients with advanced breast and colorectal cancers involves the use of broadly cytotoxic agents applied either sequentially or in various combinations and, generally, in concert with biologic agents. Although these strategies have met with laudable success, they unfortunately do not result in curing patients with disease that has spread beyond the practical limits of surgical intervention. Thus, there is an urgent need to develop more effective and better tolerated systemic therapeutic options.

In this issue of the Journal, Correale et al. describe the use of a 28-amino-acid peptide (TS/PP) that contains the sequence of three HLA-A02.01–restricted peptides derived from the enzyme thymidylate synthase (TS) to vaccinate mice against cancers that overexpress this enzyme relative to its expression in normal tissues (2). In vitro, TS/PP peptide-pulsed dendritic cells induced potent cytotoxic T-lymphocyte (CTL) antitumor activity against multiple TS-derived peptides that was enhanced by pretreating tumor cells with 5-fluorouracil (5-FU). More important, vaccination with this polypeptide in combination with relatively nontoxic doses of 5-FU induced a potent CTL response that inhibited human colon and breast cancers in vitro and cured or delayed the growth of a human lymphoma tumor cells inoculated into HLA-A02.01 transgenic mice. Of interest, vaccination and exposure to relatively nontoxic doses of 5-FU resulted in no discernable immunemediated toxic effects on normal murine tissues by histologic examination—a remarkable result if translatable into the management of human cancer.

What is TS and why was this particular enzyme selected as a potential target for vaccination? TS is expressed in virtually every normal and malignant cell and is essential for maintenance of cell viability in the absence of a supraphysiologic source of thymidine. TS is an essential step in the de novo pyrimidine synthetic pathway and responsible for the enzymatic methylation of deoxyuridylate to form thymidylate needed for DNA repair and replication. TS has been shown by multiple laboratories to be overexpressed in tumor versus normal tissues, and its cellular levels are tightly controlled by an autoregulatory translational feedback inhibition resulting from the binding of the TS protein to its own mRNA—an interaction that is exquisitely dependent on the state of occupancy of the enzyme by its substrates and/or inhibitors (3,4). With exposure to 5-FU, the enzyme becomes tightly bound in a ternary complex with the fluoropyrimidine anabolite, 5-fluorodeoxyuridylate, and methylene tetrahydrofolate, resulting in loss of its ability to bind to and negatively regulate the translation of its own mRNA. This loss of translational repression results in increased protein levels of TS. It is this induction of TS protein along with its baseline relative overexpression in cancerous cells that provided the rationale for selecting this enzyme as a vaccine target. Overexpression of TS has also been shown to be associated with a poor prognosis in patients with colon and breast cancers and with relative insensitivity to 5-FU in patients with advanced disease (5,6). Recently, it has been demonstrated that TS overexpression is oncogenic (7). Each of these features supports TS as a potential target for vaccination.

Although in vitro and in vivo murine tumor models have provided us with tremendous insight into mechanisms to enhance antitumor immunity, relatively few humans have benefited from conventional peptide-based cancer immunotherapy. Bulky tumors outgrowing or suppressing the immune response, loss of the target antigen that is not essential for tumor survival, and poor host immunity as a consequence of immuno-suppressive cytotoxic chemo/radiotherapy are all factors thought to play a role in the failure of peptide-based vaccination approaches. The ability to generate tumor antigen–specific immune responses in patients who ultimately do not achieve a disease response has led investigators to explore methods to sensitize the tumor to immune attack. Recently, radiotherapy and several cytotoxic agents have been shown to increase Fas and the expression of tumor-associated antigens such as carcinoembryonic antigen (CEA) (8). Although Correale et al. show that 5-FU sensitizes the tumor to killing by TS-specific CTL, definitive data showing that CTL killing is enhanced as a direct consequence of increased tumor surface expression of TS-derived peptide antigens are not presented in this study. An alternative explanation that needs to be considered is that the enhanced tumor susceptibility to T-cell attack is the result of another of the many cellular effects associated with exposure to 5-FU. Several laboratories have previously shown that 5-FU–exposed tumors increase the expression a variety of molecules including tumor necrosis factor–related apoptosis-inducing ligand (TRAIL), Fas, and p53—molecules that might sensitize the tumor (and possibly nonmalignant cells) more globally to other antigen-specific CTL responses (9–11). A more comprehensive understanding of the mechanism of interaction may permit the use of more tumor-selective antigens and provide a broader menu of cytotoxic agents associated with increasing the expression of the critical molecule(s). Although alternative mechanisms that may underpin the noted synergy need further investigation, this fact does not detract from the importance of the present study.

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However, the vaccine approach described by Correale et al. does raise several concerns related to potential barriers to clinical translation that will require future exploration. To optimize efficacy while avoiding autoimmunity, investigational cancer vaccine regimens have focused largely on antigens that are both overexpressed and restricted to the tumor. Although TS is highly expressed in cancer cells, it is also expressed in virtually all normal cells and may be highly induced in normal tissues with exposure to 5-FU or other inhibitors of TS such as the antifolate inhibitor, pemetrexed (Alimta), currently approved in the United States for the management of patients with malignant pleural mesothelioma and non–small-cell lung cancer (12,13). These facts provide a cautionary note to the potential for safely translating this particular vaccine target into patients despite the apparent lack of autoimmunity noted in the murine model. An additional concern is that the mice were vaccinated prior to the infusion of malignant cells and treatment with 5-FU. The ability of tumors to suppress cancer immunity and the immunosuppressive effects of chemotherapy prevent one from extrapolating whether this vaccination approach would have resulted in the same protective effect in tumor-bearing mice treated with 5-FU prior to or simultaneously with vaccination. A lack of efficacy under these latter conditions would relegate the approach to a prevention-only strategy, where the potential risk of autoimmunity may be more problematic given the global expression of TS in normal tissues. A recent report by this same group provides evidence that T-cell immunity against CEA- and TS-derived peptides in humans with metastatic colon cancer persists when combined with TS antibodies and antitumor activity in metastatic colon cancer patients. J Clin Oncol 2003;21:241–50.

In summary, the findings of Correale et al. broadly imply that 5-FU and other cytotoxic agents have the additional benefit of synergizing with tumor immunity by sensitizing the tumor to the effects of tumor antigen–specific CTL. On the basis of these data, it would seem reasonable to investigate the efficacy of postchemotherapeutic vaccination or the adoptive infusion of in vitro expanded antigen-specific CTL. Careful exploration of the logistics of drug dosing and drug timing relative to peptide vaccination or infusion of CTL with such sequential chemotherapy-regimens is needed because they will likely have a critical impact on the efficacy of such approaches. Finally, although the induction of TS may be critical to the efficacy of the described approach, further exploration of alternative mechanisms associated with exposure to 5-FU, as well as the wisdom of targeting a protein expressed in both normal and malignant cells, is needed.

REFERENCES


