Smallpox, polio and now a cancer vaccine?

Fusions of dendritic cells and renal carcinoma cells have been used as a vaccine in the effective and non-toxic treatment of patients with metastatic renal cancer. This approach may be applicable to other tumor types (pages 332–336).

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DESPITE PROGRESS IN the treatment of cancer with surgery, radiotherapy and chemotherapy, only incremental advances have been made in improving survival rates, particularly in patients with disseminated carcinomas of the breast, lung, prostate and kidney. Moreover, most cancer treatments are compromised by substantial toxicities. Advances in our understanding of antitumor immunity and the genetic alterations that accumulate in the progression to malignancy have recently provided unforeseen opportunities for the development of more selective and safer therapeutic approaches. One such strategy involves the use of dendritic-cell-based vaccines. In this issue of *Nature Medicine*, Kugler *et al.*[1] describe unprecedented regressions in patients with metastatic renal cancer using a new vaccine therapy based on fusions of dendritic cells and tumor cells[2]. Moreover, this broadly applicable approach was associated with little if any toxicity.

Cancer immunotherapy has held substantial, but mostly unfulfilled, promise over the past century. The discovery of the mechanistic basis for antigen presentation in the context of major histocompatibility complex (MHC) molecules[3], the identification of tumor antigens, and the concept of inducing a T-cell response against these antigens through 'professional' antigen-presenting cells[4] (APCs) have led us to believe that it should be possible to activate the immune system to attack a developing tumor.

The APCs most suitable for this strategy are dendritic cells (DCs), which can be distinguished from B lymphocytes and macrophages by their abundant expression of co-stimulatory molecules and ability to efficiently prime both $CD4^+$ (helper) and $CD8^+$ (cytotoxic) immunity[5]. Based on these findings, antitumor vaccines have been developed with DCs that have been pulsed or transduced to present peptides derived from tumor antigens. These approaches require the identification of a tumor antigen, and few are known at present for human tumors. Given the genomic instability associated with tumor progression, there are conceivably many epitopes unique to malignant clones that could represent targets in the activation of a tumor-specific immune response. As an approach to exploit both known and unique epitopes, DCs have been fused to carcinoma cells to generate heterokaryons, combining the machinery needed for immune stimulation with presentation of a large repertoire of tumor antigens[2].

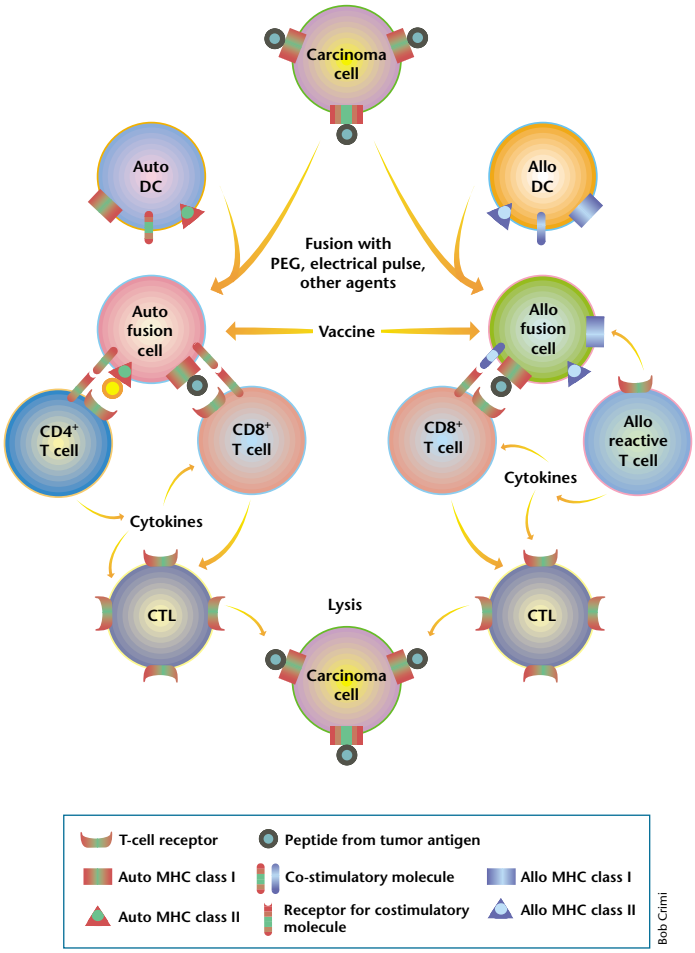

Fig. 1 A tumor vaccine is created by fusion of carcinoma cells to autologous and allogeneic dendritic cells in the presence of polyethylene glycol or an electrical pulse. As a vaccine using a patient's own tumor, the fused cells or heterokaryons directly activate $CD8^+$ T cells by presenting tumor antigens in the context of MHC class I molecules and in the presence of DC-derived co-stimulatory molecules. Autologous carcinoma–DC fusion cells (auto fusion cell) can also present tumor antigens by DC-derived MHC class II molecules and thereby stimulate helper $CD4^+$ T cells. In fusions of carcinoma cells and allogeneic DC (Allo fusion cell), presentation of tumor antigens to autologous T cells is dependent on expression of tumor-derived MHC molecules. In contrast to the autologous fusions, heterokaryons of carcinoma-allogeneic DCs can stimulate alloreactive T cells. The release of cytokines by $CD4^+$ or alloreactive T cells can contribute to the activation and proliferation of cytotoxic T lymphocytes, which lyse tumor targets. DC, dendritic cell; PEG, polyethylene glycol; CTL, cytotoxic T lymphocyte.

For decades, cell biologists have been using polyethylene glycol or electrical stimulation to fuse membranes of two distinct cells and generate heterokaryons. Kohler and Milstein used cell fusion to form B lymphocyte and myeloma cell heterokaryons that produce monoclonal antibodies[6]. Activated B lymphocytes[7] and B-lymphoma cells[8] have also been fused to carcinoma cells in attempts to develop antitumor vaccines. However, in developing DC-based heterokaryons, one can take advantage of the accessibility of human DCs from peripheral blood and the unique ability of DCs to prime naive cytotoxic T lymphocytes (CTLs) *in vivo*. In animal tumor models, the fusion of DCs to carcinomas[2] and to other types of tumor cells has proven effective in causing host rejection of established local and metastatic tumors. Immunization with a DC–tumor cell fusion vaccine has also been shown to reverse immunologic unresponsiveness to the human DF3/Muc1 tumor-associated

antigen in Muc1-transgenic mice[9]. Moreover, there has been no evidence of normal tissue toxicity from the DC fusion cell vaccines.

Kugler and colleagues have now developed a therapeutic vaccine for patients with metastatic renal cell cancer by fusing DCs and autologous tumor cells with an electrical pulse. Response rates in the treatment of metastatic renal cell cancer with chemotherapeutic or hormonal agents are less than 10%. Disease regressions have also been demonstrated in only a minority of patients treated with interferons or interleukin-2. Here, the authors report tumor responses in seven of seventeen patients vaccinated with the fusion cells and prolonged stabilization of disease in two additional patients. Four patients achieved complete regression of their disease and have had no evidence of recurrence for periods of up to 21 months. In these patients, regressions were found in diverse metastatic sites and involved large tumor masses. Other than mild, transient fever, and pain at metastatic sites, there were no adverse effects. In addition, there was no evidence of autoimmune disease. As the authors point out, their provocative findings were obtained in a small cohort of patients and longer follow-up is needed to fully assess the effect of the vaccine. Nonetheless, the substantial regressions often seen within weeks of the first immunization indicate the potency of these vaccines and the responsiveness of the immune system to an adequate stimulus.

There are many experimental issues raised by the study of Kugler *et al.* that relate to the development of an optimal fusion cell vaccine. The authors used autologous tumor cells that had been fused to allogeneic DCs from random donors. Allogeneic stimulation of autologous T cells could contribute to induction of the immune response to the tumor (Fig. 1). In contrast, fusions with autologous DCs may be more effective in targeting tumor cells with downregulated expression of MHC molecules (Fig. 1). Fusion cell dosages and the number of vaccinations required represent additional variables that will need to be optimized in future studies. In cases of a mixed response or progressive disease, fusions with the different tumor metastases, which could be clonal, may also be required to achieve a complete response. Additionally, it will be important to determine whether fusion cell vaccines can induce immunity against multiple tumor antigens, and prevent tumor cell escape by antigen downregulation. It will also be important to identify the tumor antigens that best stimulate a potent anti-tumor response. Kugler *et al.* have already begun to address this issue by demonstrating that the fusion cell vaccine induces CTL activity against the Muc1 antigen, which is widely overexpressed in breast and other carcinomas[10].

If confirmed, the results of this study represent an unprecedented advance in the selective and non-toxic immunotherapy of a disseminated and lethal carcinoma. In addition to the potential benefits for patients with metastatic renal cell cancer, the findings should provide the impetus for assessing effectiveness of fusion cell vaccines in the treatment of other tumors. The immunotherapy of renal cell or other cancers with fusion cell vaccines could contribute to fulfilling the promise that emanated from the work of Jenner and has been anticipated from the success of vaccines against smallpox, polio and other infectious diseases.

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Sane genetics for schizophrenia

Although past epidemiological studies have supported the theory that there is a genetic component to schizophrenia, the genetic data have been inconsistent. However, an overall analysis indicates several chromosome regions with good candidate genes for schizophrenia susceptibility.

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DESPITE GREAT RESISTANCE to the theory that there is a genetic basis for psychiatric disease, epidemiological studies over the past 30 years have consistently demonstrated that genetic factors are important in the etiology of schizophrenia. Repeated analyses of family, adoption and twin data sets suggest a 10-fold increase in lifetime risk for relatives of schizophrenics. Additionally, 'adopted-away' children have the same risk as their biological (rather than their environmental) families, and concordance among monozygotic twins is approximately 50% (ref.1).

Twin studies also show that susceptibility to schizophrenia has a non-genetic component—monozygotic twins are not 100% concordant, and dizygotic twins (genetic siblings) have about twice the risk of developing schizophrenia of ordinary siblings. Analysis of concordance in first-, second- and third-degree relatives suggests that variants at three or more separate loci are required to confer susceptibility, and that these allelic variants increase risk in a multiplicative rather than additive manner, with the total risk being greater than the sum of the indi-