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INVITED REVIEW

Vaccine-based approaches to squamous cell carcinoma of the head and neck

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Vaccine-based approaches for the treatment of advanced squamous cell carcinoma of the head and neck have achieved very limited success. Improvement in vaccine efficacy for both diseases control and survival is predicated on a careful analysis of the root causes for successes and failures to date. In this review, we analyse the utility and limitations of select protective and therapeutic vaccine strategies for tumour prevention and therapy. Based on this characterisation, we define potential directions which are meritorious of future study.
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Introduction

The treatment of squamous cell carcinoma of the head and neck (SCCHN) has witnessed significant advances in the past decade which have fundamentally altered the means by which clinicians approach this disease. For example, in select settings, chemoradiation is now considered one standard of care for advanced lesions of the oropharynx or larynx with loco-regional metastases (Forastiere *et al*, 2003; Bernier *et al*, 2004; Cooper *et al*, 2004). Furthermore, there is a burgeoning of targeted therapeutics (e.g. erbitux) which are currently approved or in advanced-stage clinical trials for the treatment of SCCHN (Baselga *et al*, 2005; Burtness *et al*, 2005; Bonner *et al*, 2006). While these strategies each serve as important tools in the armamentarium of the head and neck oncology team, their impact on overall survival has been, at best, incremental (Forastiere *et al*, 2003). Of equal import, it is now becoming increasingly clear that these approaches, particularly those relying on a combination of chemotherapy and radiation therapy, are fraught with long-term sequelae, the impact of which on quality of life is not as of yet fully determined (Eisbruch *et al*, 2002; El-Deiry *et al*, 2005; Terrell *et al*, 2004).

In order to improve both the survival and quality of life of patients with SCCHN, surgical, medical, and radiation oncologists must explore new therapeutic approaches in the setting of well-controlled clinical trials. It is critical that basic scientists and clinicians work together in concert to insure that problems faced in the laboratory reflect realistic clinical need and the solutions developed are sufficiently concrete to be translated into clinical practice. Furthermore, these strategies must be implemented in such a way that embraces both traditional and non-traditional forms of support, including philanthropic gifts and academic industrial partnerships. Finally, success in this venture will be predicated on an improved understanding of each individual patient's needs as a means of increasing trial participation and insuring the highest quality of care. In this review, we address the potential utility of vaccine-based approaches for the treatment of SCCHN.

Historical perspective

The foundation of T-cell cancer immunotherapy is based on classical studies by Prehn and Main (1953, 1954, 1957). Early experiments demonstrated that mice are capable of generating cellular-based tumor-specific immunity to select tumors, and that adoptive transfer of cells from these animals can protect naïve mice from tumor challenge (Prehn and Main, 1957). Exhaustive animal studies, including studies by our group, utilizing a variety of vaccine-based approaches, have confirmed that the cellular immune response is a potent effector mechanism against murine tumors (Boczkowski *et al*, 1996; Gilboa *et al*, 1998; Pardoll, 1998; Strome *et al*, 2002). Vaccine-based approaches for the treatment of established malignancies in humans, however, have achieved little success and few have progressed beyond phase I trials. In fact, a recent analysis of tumor vaccine studies conducted by the National Cancer Institute revealed a meager overall response rate of 2.6% (Rosenberg *et al*, 2004). These data suggest that it is

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time to re-evaluate the utility of vaccine-based immunotherapy by focusing on successes and failures as a means to best define future direction.

Successful cancer immunotherapy: prevention, active immunity, and adoptive cell transfer

If successful immunotherapy is defined as the ability to limit disease acquisition or mediate the regression of established cancer, three approaches are particularly noteworthy. The first involves the use of viral-like particle (VLP)-based vaccines for the prevention of cancer of the uterine cervix in at-risk populations. VLPs have demonstrated protective humoral immunity and have also recently proven to be highly effective in stimulating both CD4 and cytotoxic T-lymphocyte (CTL) responses (Schirmbeck and et al., 1996; Paliard and et al., 2000; Murata and et al., 2003; Parez *et al*, 2006). Specifically, two recent studies have demonstrated that human papillomavirus (HPV)-type-specific VLPs can prevent HPV infection, an independent risk factor for cervical cancer, in at-risk women (Koutsky *et al*, 2002; Harper *et al*, 2004). Given the established association between HPV16 and head and neck malignancies, the widespread use of VLPs for the treatment of cancer of the uterine cervix may also have concomitant benefits on the prevention of SCCHN.

Three points regarding the use of VLPs for immunotherapy are particularly relevant to the design of subsequent clinical trials for SCCHN. First, the success of VLPs rests on an ability to stimulate antibody-mediated immunity against specific HPV subtypes and not necessarily stimulation of the cellular immune response. In this sense, we are only requiring the immune system to perform activities within its normal scope of function. Secondly, in the trials with VLPs, the immune system must play only a protective rather than therapeutic role. Finally, it is important to realize that while this approach will likely have implications on the treatment of HPV-based benign and malignant disease, several years will be required before its potential can be fully realized (Steinbrook, 2006).

The second vaccine-based approach demonstrating clinical efficacy in select circumstances involves the use of autologous dendritic cells for the induction of an active, anti-tumor immune response. Dendritic cells (DC) are potent antigen-presenting cells found throughout the skin, upper respiratory tract, lungs, and gastrointestinal (GI) tract. Various pathogens, dead or apoptotic cells, and other antigens can be processed and presented by DC. These activated cells can migrate to lymphoid tissues where they interact with T and B cells, and effectively shape the immune response (Banchereau and Steinman, 1998). In fact, murine studies on SCCHN have demonstrated the potent capacity of DC to induce antigen-specific anti-tumor immunity when pulsed with apoptotic tumor cells and activated with interleukin-2 activation (Son *et al*, 2002).

Recent studies have shown that DC primed with tumor antigens can also stimulate clinically meaningful antigen-specific immune responses, resulting in the regression of both established carcinomas and hematologic malignancies (Hsu *et al*, 1996; Kugler *et al*, 2000; Davis *et al*, 2001; Weng *et al*, 2004; Redfern *et al*, 2006). For example, in patients with cutaneous T-cell lymphoma, Maier *et al* (2003) reported a tumor-specific delayed-type hypersensitivity response (DTH), an indicator of antigen-specific cellular immunity, in 100% of patients treated with DC pulsed with whole-tumor lysate; and five of 10 of patients achieved an objective clinical response. For patients with metastatic melanoma, Nestle *et al* (1998) utilized DC pulsed with tumor lysate or a cocktail of peptides recognized by CTL to achieve an objective clinical response in five of 16 patients with a complete eradication of disease noted in two.

Several points are noteworthy when considering DC-based strategies for the treatment or prevention of SCCHN. As these are cellular products they are subject to individual patient variability, including differences in culture methods, loading strategies, and injection techniques. A lack of product uniformity limits the utility of this approach for phase II/III studies. Additionally, it is difficult to harvest sterile tumor from patients with SCCHN, even from the neck, complicating potential loading strategies. Therefore, while it is clear that monocyte-derived DC primed with peptide antigen or irradiated whole tumor can be used to initiate potent antitumor-specific immunity, various translational barriers such as tumor processing, DC harvest, and cell culture pose formidable challenges to large-scale clinical implementation.

The third example of 'successful' immunotherapy is the passive transfer of T cells, known as adoptive cell transfer therapy (ACT). This technique relies on the *ex vivo* activation and expansion of tumor-reactive lymphocytes which are then returned to the host. Murine models have clearly defined the ability of ACT to mediate the regression of poorly immunogenic established tumors (Eberlein *et al*, 1982; Rosenberg *et al*, 1986; Overwijk *et al*, 1998). However, similar strategies proved difficult to transfer into the clinical setting, with early studies demonstrating only limited success (Rosenberg and Terry, 1977; Rosenberg *et al*, 1994; Yee *et al*, 2000; Dudley *et al*, 2001, 2002b). In order to improve the persistence and *in vivo* activity of the transferred cells, recent approaches have evaluated various chemotherapies to deplete the immune system of endogenous T-cell subpopulations that are recognized to suppress immune function (e.g. naturally occurring T regulatory cells) or limit the physical space required for transferred cells to engraft and expand (North, 1982; Dudley *et al*, 2002b). Using a regimen composed of cyclophosphamide and fludarabine, Dudley *et al* (2002) reported clinical success with the adoptive transfer of highly active T cells directed against self antigens in patients with metastatic melanoma. Long-lasting effector T-cell clones displayed functional activity and appropriate tumor migratory patterns. Clinically, these cells effectively mediated the regression of bulky metastases. Since this seminal report, Dudley *et al* (2005) have increased their treatment group to 35 and have

demonstrated objective clinical responses in over 50% of patients (Robbins *et al*, 2004; Dudley *et al*, 2005).

Several points should be noted regarding ACT. The studies performed by Dudley *et al* (2005) clearly demonstrate the ability of adoptively transferred T cells to mediate tumor regression in the setting of bulky metastatic disease and arguably offers proof, that for the first time in humans, ACT is a viable therapeutic strategy. Importantly, however, results were achieved in the setting of a combined approach where chemotherapy was employed initially as an immunomodulatory agent. Furthermore, these trials were performed at a highly specialized center, potentially limiting the utility of this strategy to be evaluated in advanced-stage clinical trials.

Cancer vaccines: the future

As we evaluate these examples of 'successful' immunotherapy, several recurring principles come to light which should serve as guidelines for the development of new immunotherapeutic approaches. First, based on the VLP data, it is clear that significant success can be achieved when vaccines are employed for the prevention rather than the treatment of established disease. While trials to evaluate prevention may require greater numbers of participants, longer follow-up to evaluate meaningful endpoints, and raise different ethical issues than therapeutic studies, it is the authors' opinion that these hurdles must be overcome if the value of immunotherapy is to be realized. Secondly, although cellular-based vaccines can stimulate clinically meaningful antitumor responses, their wide-scale evaluation and clinical application is limited by factors such as product uniformity and the significant resources necessary for successful production. In this sense, it will be important to overcome the technology barriers which have hindered the development of T-cell-based vaccines as standardized reagents. Finally, when used in the therapeutic setting, it is now clear that antitumor immunity can be augmented by ancillary approaches such as the use of chemotherapeutics or molecules which regulate costimulatory function. Alternatively, it may be possible to overcome tumor-mediated immune tolerance by sensitizing select populations of memory T cells which have different phenotypic and functional attributes (Allison, 1994; Maier *et al*, 2003; Phan *et al*, 2003; Ribas *et al*, 2005). In order to accomplish these endpoints, this discussion will touch upon three strategies: (1) the use of peptide vaccines, (2) the use of costimulatory molecules, and (3) novel routes of vaccine administration.

Development of vaccines as drugs

The future success of immunotherapy will likely be predicated on the development of standardized vaccines which can be evaluated in multi-institutional studies. Within the past several years, it has become clear that SCCHN expresses several tumor-associated and tumor-specific antigens, and the human leukocyte antigen (HLA)-restricted antigenic epitopes for many of these molecules have now been characterized (Hoffman *et al*, 2004). These data afford the opportunity to develop peptide or whole protein-based vaccines which can be translated into large-scale clinical trials. For example, in response to promising animal data and clinical studies demonstrating the presence of HPV in SCCHN (Albers *et al*, 2005), our group has designed a multi-epitope vaccine using MAGE-A3 and HPV-16 Trojan peptides. These vaccines contain both CD4 and CD8 epitopes fused by furin-cleavable linkers which are cleaved and individually released in the Golgi by furin-specific endopeptidases (Lu *et al*, 2001, 2004). Additionally, these vaccines incorporate HIV TAT translocating regions, shown to enhance transmembrane delivery of large peptides and to render resistance to cellular proteolysis and degradation (Becker-Hapak *et al*, 2001; Lu *et al*, 2004; Wadia and Dowdy, 2005). These peptides are currently being evaluated in a phase I clinical trial in which they are administered to HLA-A2-positive patients with advanced SCCHN who express HLA-A2 on both peripheral blood mononuclear cell (PBMC) and tumor. Completion of this clinical trial will have important implications on vaccine therapy for SCCHN.

When considering the future of peptide-based vaccines, it is important to recognize that limitations such as HLA restriction criteria and the need for tumors to express the desired target are significant impediments to patient eligibility. Therefore, peptide-based vaccines should simply be viewed as one example of a targeted intervention that will likely require further study prior to wide-scale application. Additionally, when employed in the therapeutic arena, it is likely that such reagents will be most successful when used in combination with biologics that can enhance effector function.

Costimulation

One potent means to modulate the effector function of the antitumor immune response is through the manipulation of defined costimulatory pathways. Generation of an effective T-cell immune response requires two signals: (1) an antigen-specific interaction that occurs through peptide presentation in the context of an appropriate HLA molecule, and (2) a second antigen-independent costimulatory signal. Perhaps the best characterized costimulatory pathway is CD28/B7. B7 binding with CD28 on the surface of T cells promotes cellular activation, proliferation, and the prevention of cell death (Allison, 1994; Manickasingham *et al*, 1998). In contrast, B7 binding to the CTLA-4 counter receptor inhibits proliferation (Chen, 2004; Zou, 2005). Manipulation of these receptor/ligand pairs has profound therapeutic implications with recent clinical studies demonstrating that blockade of CTLA-4 can stimulate the regression of human malignancies (Phan *et al*, 2003; Ribas *et al*, 2005). While such progress has been encouraging, a study earlier this year in the UK using a synthetic monoclonal antibody targeted against CD28, met with disastrous results, reminding us that manipulation of costimulatory pathways is a double-edged

sword (Cho, 2006). Importantly, however, such results should not deter the progress of appropriately designed clinical trials with adequate oversight and monitoring as the authors believe that manipulation of these pathways have enormous potential to ameliorate human disease. The role of costimulation is reviewed elsewhere (Kremer *et al*, 2003; Bour-Jordan *et al*, 2004; Strome and Chen, 2004).

Vaccination route

In addition to standardizing the reagents for immunotherapy and utilizing combinatorial approaches, modification of the route of vaccine delivery may hold promise as a means of enhancing vaccine efficacy. Classical antimicrobial vaccination strategies have relied on subcutaneous or intramuscular injections to stimulate long-lasting immunity. It is now clear however that the route of vaccination impacts both the potency and location of immune response generated. Studies in mice have revealed that subcutaneously injected DC migrate toward draining lymph nodes and initiate T-cell responses whereas intravenously administered DC do not (Lappin *et al*, 1999). Furthermore, when compared with intravenously injected DC, cells injected intracutaneously home toward inflamed skin better, and those injected intraperitoneally home toward the gut better (Dudda *et al*, 2004). In a mouse tumor model, intratumoral boosting shots produce better antigen-specific T-cell responses than subcutaneous injections do alone (Kudo-Saito *et al*, 2005). Clinically, various studies have shown that intranodal and intralymphatic injections of DC (Bedrosian *et al*, 2003), autologous tumor cells (Williams *et al*, 1992), and DNA vaccines (Tagawa *et al*, 2003) have yielded improved CTL responses in cancer patients. Currently, however, only a small number of studies have correlated vaccination route with memory T-cell function, and there is no published data regarding the bone marrow (BM) as a potential site for cancer immunization.

BM in cancer immunity

Recent investigations, including our own, provide new evidence that the BM serves as an enclave for memory T cells with a unique ability to respond to recall antigens (Slifka *et al*, 1997; Becker *et al*, 2005; Mazo *et al*, 2005; Parretta *et al*, 2005; Zhang *et al*, 2006). Secondary immune responses by memory T cells are faster and more potent than primary responses, enabling rapid protection from viral reinfection. Recent studies suggest that the BM is the preferred site for migration, proliferation, and retention of memory T cells responsive to tumor antigens as well (Becker *et al*, 2005). In breast cancer patients with disseminated tumor, the BM contains far more memory T cells than that of healthy controls; and moreover, these cells correlate with tumor size (Feuerer *et al*, 2001a). Neoplastic cells in the BM may provide a source of antigen for a mixed population of mature and immature resident DC better aimed at priming naïve T cells through enhanced antigen presentation and costimulatory signaling capabilities (Bai *et al*, 2003).

Tumor vaccine studies in mouse models have shown that the presence of live tumor cells in the BM is associated with systemic protection from tumor-specific challenge (Khazaie *et al*, 1994; Muller *et al*, 1998). Adoptive transfer of tumor-specific BM-derived memory T cells from breast cancer patients caused the regression of autologous tumor xenotransplants in NOD/SCID mice (Feuerer *et al*, 2001b). Currently, a phase I clinical trial is ongoing in the Department of Gynecology at the University Hospital of Heidelberg for evaluating the feasibility of BM-derived re-activated autologous memory T cells for immunotherapy in advanced breast cancer patients (Schirrmacher *et al*, 2003). Taken together, the BM may represent an optimal setting for the stimulation and maintenance of a potent antitumor immune response.

Novel directions and potential therapeutics

In summary, T-cell-based immunotherapy for the treatment of cancer has failed to produce durable therapeutic results in the vast majority of cases. While multiple studies have shown that tumor vaccines can produce antigen-specific T-cell immunity, few have produced objective clinical evidence of tumor regression. However, successful cancer immunotherapies, including VLPs, dendritic cells, and adoptive T-cell transfer following immunodepletion have paved the way for further study. Future directions as discussed will likely explore: (1) standardized vaccines to stimulate T-cell immunity, (2) combinatorial therapies, and (3) novel routes for vaccination delivery.

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