The Veterinary Journal xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

The Veterinary Journal

journal homepage: www.elsevier.com/locate/tvjl

Review

Cancer vaccines: Harnessing the potential of anti-tumor immunity

Mark A. Suckow *

400 Freimann Life Science Center, University of Notre Dame, Notre Dame, IN 46556, United States

ARTICLE INFO

Article history:
Accepted 10 June 2013
Available online xxxx

Keywords:
Cancer
Immunity
Dog
Vaccine
Tyrosinase
Tumor stroma

ABSTRACT

Although the presence of cancer suggests failure of the immune system to protect against development of tumors, the possibility that immunity can be redirected and focused to generate an anti-tumor response offers great translational possibility. The key to this is identifying antigens likely to be present in any given tumor and functionally critical to tumor survival and growth. Such tumor-associated antigens (TAAs) are varied and optimally should be absent from normal tissue. Of particular interest are TAAs associated with the tumor stroma, as immunity directed against the stroma may restrict the ability of the tumor to grow and metastasize. Important to directing the immune system toward an effect anti-tumor response is the understanding of how TAAs are processed and how the tumor is able to evade immune elimination. The process of immunoediting happens in response to the selective pressure that the immune system places upon tumor cell populations and allows for emergence of tumor cells capable of escaping immune destruction.

Efforts to harness the immune system for clinical application has been aided by vaccines based on purified recombinant protein or nucleic acid TAAs. For example, a vaccine for canine melanoma has been developed and approved based on immunization with DNA components of tyrosinase, a glycoprotein essential to melanin synthesis. The performance of cancer vaccines has been aided in some cases when supplemented with immunostimulatory molecules such as interleukin 2 or a novel extracellular matrix vaccine adjuvant. Vaccines with the broadest menu of antigenic targets may be those most likely to succeed against cancer. For this reason, tissue vaccines produced from harvested tumor material may offer significant benefit. With several cancer vaccines on the veterinary and human markets, efforts to understand basic tumor immunology are soon to yield great dividends.

Introduction

The idea that the immune system plays a critical role in protecting the host from cancer originated with Paul Ehrlich early in the 20th century (Ehrlich, 1909) and anti-tumor immune responses remain a subject of considerable interest as the idea of using immunotherapy for the treatment of cancer has gained greater acceptance. Although complex, several key components of the immune response to tumors have been defined and studied, with the cytotoxic T lymphocyte response being identified as a critical link among these components. Interestingly, while cells associated with the immune system can inhibit tumor growth and progression, immune responses sometimes promote tumor cell growth and survival through induction of inflammation (Dougan and Dranoff, 2009; Chow et al., 2012).

Tumor antigens and immune responses

Most tumor cells express antigens that are not found on normal cells. These tumor-associated antigens (TAAs) come from several sources, including oncogenic viruses, expression of oncogenes or mutated oncosupressors, or expression of mutated genes. As an example, melanoma is characterized by the expression of several TAAs, including gp100, tyrosinase, MAGE-A1, and NY-ESO (Dunn et al., 2007; Pandolfi et al., 2008). Colorectal tumor cells often express carcinoembryonic antigen (CEA), a glycoprotein involved in cell adhesion. Though CEA is normally present during fetal development, it is absent from normal adult tissue; however, CEA expression correlates with progression of colorectal cancer, and has been used as a clinical marker of the disease (Boghossian et al., 2011; Mazurek et al., 2011).

Because tumor tissue is characterized by a variety of antigens not typically found in normal tissue, the immune system may mount a protective response. Innate immunity against the tumor is invoked very quickly, as macrophages which are innately programmed to attack and destroy tumor cells much in the same fashion that they eliminate invading pathogens, are drawn to the

* Tel.: +1 574 631 6085.
E-mail address: Suckow.1@nd.edu

1090-0233/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tvjl.2013.06.005

tumor. Likewise, granulocytes such as polymorphonuclear leukocytes serve not only as effector cells in anti-tumor immunity, but also as a source of cytokines which are involved in the activation and regulation of effector cells of the adaptive immune system (Mantovani et al., 2011).

With time, adaptive anti-tumor immune responses develop. Dendritic cells migrate to the tumor as part of the innate immune response and serve as a link between innate and adaptive immunity. After processing tumor antigens, dendritic cells stimulate specific immune responses by directly interacting with T and B lymphocytes and by releasing cytokines that further stimulate the immune response. As with immune responses to infectious pathogens, both cell-mediated and humoral adaptive immunity may be invoked. Cell-mediated immunity represents the primary means by which tumors are attacked by the immune system.

The initial response of the immune system to a tumor is to recruit lymphocytes in an attempt to clear the tumor. These tumor-infiltrating lymphocytes (TILs) include cytotoxic T lymphocytes (CTLs), helper T cells, and natural killer (NK) cells. A common process by which immune rejection of tumor tissue occurs begins with presentation of TAAs to major histocompatibility complex (MHC) class I molecules present on the surface of TILs. Because CTLs are particularly abundant among TILs, this process may result in a robust anti-tumor immune response when substantial amounts of TAAs are present (Bennett et al., 1992; Hishii et al., 1997). When CTLs are activated, the death activator Fas ligand is expressed on the CTL surface and apoptosis of tumor cells results via the Fas/FasL pathway (Giovannetti et al., 2008; Rippo et al., 2010). Alternatively, CTLs may induce apoptosis using a Fas-independent pathway, specifically the granzyme-mediated pathway which involves the release of serine esterases which induce fragmentation of DNA in target cells (Groscurth and Filgueira, 1998).

Upon recognizing tumor cells as abnormal through interaction with TAAs, CTLs are the first to attack the tumor and represent a primary anti-tumor defense. NK cells are derived from the common lymphocyte progenitor and are part of the innate immune system. Both CTLs and NK cells directly destroy tumor cells after recognizing changes in MHC class I surface molecules of tumor cells. Helper T cells interact MHC class II molecules on the surface of tumor cells and are then stimulated to release cytokines which enhance the activity of CTLs and macrophages. Further, surface molecules such as CD40 are upregulated in the helper T cell, which can then interact with B lymphocytes, thereby stimulating humoral immunity. In total, the cellular response to a tumor consists of multiple players on a team which, if vigorous and coordinated, can eliminate the tumor.

Coordination of the anti-tumor response requires communication between cells of the immune system. Cytokines represent the language that permits the immune cells to organize a successful attack (Dranoff, 2004). For example, interleukin (IL)-6, produced by T lymphocytes and macrophages, enhances the proliferation of both T and B lymphocytes. Granulocyte macrophage colony-stimulating factor (GM-CSF) is produced by T lymphocytes, NK cells, and macrophages and enhances tumor antigen presentation to lymphocytes. Likewise, gamma-interferon (IFN-γ) is produced by NK cells, T lymphocytes, macrophages, and B lymphocytes and enhances both tumor antigen presentation and cell-mediated cytotoxicity. The interplay of cytokines and effector cells is complex, as demonstrated by transforming growth factor (TGF)-β, which has a cytostatic effect on normal cells but a mitogenic effect on tumor cells (Meulmeester and ten Dijke, 2011). An exhaustive description of the role of cytokines in tumor immunity is beyond the scope of this review.

Proteins that are associated with tumorigenesis or malignant growth may stimulate not only cellular immunity, but also humoral immunity. For example, serum antibody to the TAAs, HER2, p53, and MUC1, have all been found in breast cancer patients with tumors expressing those antigens (Lu et al., 2008). HER2 is a tyrosine kinase which plays a critical role in cellular growth and is upregulated in many cancers, including breast carcinoma. Patients with HER2-overexpressing metastatic breast cancer and vaccinated with a recombinant protein consisting of extracellular domain and a portion of the intracellular domain of HER2, and administered the HER2 kinase inhibitor, lapatinib, demonstrated anti-HER2 serum antibody with downstream signaling inhibition of HER2-expressing tumor cells (Hamilton et al., 2012). This approach was evaluated as a treatment for patients previously treated with, and who subsequently developed resistance to, the anti-HER2 monoclonal antibody, trastuzumab. Patients developed anti-HER2 antibody responses and disease progression was delayed by 55 days. However, these studies demonstrated that, although humoral immunity may offer some initial benefit, inhibition of disease progression may require multimodal approaches to therapy.

An emerging body of evidence shows that dynamic epithelial–stromal interactions in solid tumors may select subsets of stromal cells with the ability to modulate tumor behavior, and the local microenvironment promotes emergence of tumor-associated stromal cells with functions different from the normal stroma (Briest et al., 2012). For example, fibroblasts derived from breast tumors stimulated morphogenesis and growth of breast pre-neoplastic epithelial cells, while fibroblasts derived from normal breast tissue inhibited this process (Shekhar et al., 2001). Such functional changes in tumor stroma may partly be derived from the changes in secretion of growth factors and in the extracellular matrix (Schor and Scor, 2001; Haslam and Woodward, 2003).

The predominant cell type within tumor stroma is the fibroblast. Further, cancer-associated fibroblasts produce a number of factors which promote proliferation and progression of cancer. Among these factors are osteonectin, vascular endothelial growth factor (VEGF), and matrix metalloproteinases (MMPs) (Räsänen and Vaheri, 2010). VEGF, for example, has been implicated in a number of aspects of cancer growth, including angiogenesis, remodeling of the extracellular matrix, generation of inflammatory cytokines, and hematopoietic stem cell development. However, because many of these moieties are widely produced by normal cells, the immune system wisely restricts itself from attacking these otherwise inviting targets.

Important to the innate immune response to tumors are a type of pattern recognition receptor referred to as toll-like receptors (TLRs) which are localized on the membranes of both immune and tumor cells, as well as fibroblasts and endothelial cells associated with the tumor stroma (Goutagny et al., 2012). The ligands recognized by TLRs are varied and include bacterial DNA and endotoxin, and viral RNA. For reasons not understood, some TLRs are often upregulated on some types of tumor cells. For example, TLR4 is upregulated in ovarian, colon, and head and neck tumors (Huang et al., 2005; Kelly et al., 2006; Szczepanski et al., 2009). Triggering of TLRs via administration of appropriate ligands has been observed to initiate anti-cancer responses and TLRs are being studied in clinical trials primarily for their adjuvant activity. It appears that TLR activation may result in enhancement of antigen uptake, processing, and presentation by dendritic cells, thus contributing to the activation of antigen-specific T cells (Iwasaki and Medzhitov, 2004).

More specifically, circulating (plasmacytoid) dendritic cells selectively express TLR7 and TLR9 and when activated produce interferons that subsequently activate tissue dendritic cells, T and B lymphocytes, and NK cells (Palma et al., 2012); thus, activated circulating dendritic cells potentially yield significant downstream anti-tumor activity. This feature has been exploited as a means of therapeutic cancer vaccination. For example, the sipuleucel-T vaccine for human prostate cancer is prepared from

Please cite this article in press as: Suckow, M.A. Cancer vaccines: Harnessing the potential of anti-tumor immunity. The Veterinary Journal (2013), http://dx.doi.org/10.1016/j.tvjl.2013.06.005

autologous antigen presenting dendritic cells harvested from patient peripheral blood and which are incubated with a recombinant fusion protein composed of prostatic acid phosphatase and GM-CSF. The cells are incubated with the fusion protein to allow activation via TLRs present on the dendritic cells, after which they are infused back into the patient.

Evading the immune response

The presence of a tumor serves as evidence that cancerous cells have successfully avoided immune elimination. Immune selection pressure may favor growth of tumors which are less immunogenic, a process referred to as 'cancer immunoediting' (Dunn et al., 2002). Immunoediting is composed of three distinct phases: elimination, equilibrium, and escape. In the elimination phase, the innate and adaptive arms of the immune system work in tandem in an attempt to eliminate the tumor. This phase may be triggered by signals which notify the immune system that activation is needed against the tumor (Sims et al., 2009). The source of these signals is not entirely understood, however they may arise from transformed or dying tumor cells. The elimination phase occurs early during tumor growth and, if of sufficient magnitude, can destroy the neoplastic cells before a clinically apparent tumor occurs. This phase is characterized by production of IFN-γ and cytotoxic T cells. For example, it was demonstrated that mice lacking T cells and deficient in IFN-γ have greater susceptibility to spontaneous tumorigenesis (Dunn et al., 2004; Swann and Smyth, 2007). The elimination phase further includes infiltration of the tumor tissue with immune cells, including polymorphonuclear leukocytes, macrophages, lymphocytes, and in some cases eosinophils.

In the equilibrium phase of immunoediting, a tumor has been established, and a battle with the immune system rages in which the interaction between immune cells and tumor cells results in ongoing elimination of tumor cells, but with the emergence of tumor cell variants capable of avoiding immune elimination. In the equilibrium phase, a balance is reached in which tumor destruction matches with tumor growth. However, the selection pressure placed on tumor cells during the equilibrium phase largely results from the efforts of adaptive immunity; and this pressure results in selection and survival of tumor cells with reduced immunogenicity.

In the escape phase of immunoediting, tumor cells may become resistant to the effects of adaptive immunity, including cytotoxic cells. In general, escape can be accomplished by tumors in several ways: (1) alterations in antigen processing and presentation resulting in an antigen menu that is no longer recognizable as a cue for attack by the immune system; (2) production of immunosuppressive cytokines by tumor cells, and (3) generation or activation by tumors of immune-suppressive T cell populations. In the case of altered antigen processing and presentation, selective pressure may favor survival of tumor cells which do not express targeted antigens. For example, in a study of patients with metastatic melanoma who received adoptive transfer of T lymphocytes specific to the TAAs MART-1/MelanA and gp100, 3/5 patients had specific loss of the tumor antigens targeted during treatment (Yee et al., 2002).

Tumor cells may also escape destruction through expression of anti-apoptotic molecules (Reed, 1999). Likewise, factors such as VEGF, soluble Fas, TGF-β, and indoleamine 2,3-dioxygenase which are produced by tumor cells and tumor stroma can suppress the anti-tumor immune response (Ben-Baruch, 2006; Whiteside, 2006). Tumor cells are rapidly coated with platelets as they travel through the blood, thus promoting tumor cell survival and metastasis, with one mechanism involving inhibition of NK cell activity (Placke et al., 2012). Finally, recruitment of immunosuppressive regulatory T cells and myeloid-derived suppressor cells is a further mechanism used by many tumors to escape destruction (Zou, 2006; Ostrand-Rosenberg and Sinha, 2009).

Studies in mice demonstrated the failure of hosts to eliminate transplanted tumors resulted from the activity of $CD4^+$ $CD25^+$ regulatory T cells, and that depletion of these cells using an anti-CD25 monoclonal antibody enabled mice to reject the tumors (Onizuka et al., 1999; Shimizu et al., 1999). Tumors are frequently in the escape phase when clinically detected, and this is an important reason explaining why patients with tumors often lack effective anti-tumor immunity.

Role of the tumor stroma

Tumor stromal cells create an environment in which neoplastic cells are exposed to growth factors while avoiding immune recognition. This is accomplished by elaboration of cytokines which promote chronic inflammation and events leading to immune tolerance. For example, thrombospondin-1 is produced by stromal cells and leads to immune suppression via activation of TGF-β (Silze et al., 2004). There is also an abundance of evidence suggesting that during tumor formation stromal elements 'hide' or protect erroneously proliferating cells from destruction by the immune system. Via induction of local hypoxia, deregulated cytokines, and a reduction in the local pH, the tumor microenvironment appears to quiet adaptive immune responses normally generated by TAAs of malignant cells (Henning et al., 2004; Balkwill et al., 2005).

Tumor regression fails to consistently occur even in the presence of upregulated peripheral T-cell responses (Singh et al., 1992; Gajewski et al., 2006), substantiating the belief that trafficking of T-cells directly to malignant cells is inhibited by aspects of tumor stroma. Other studies have shown that even when local trafficking of T-cells is functional, the stroma is still capable of limiting T-cell effector function (Perdrizet et al., 1990; Ganss et al., 2004; Frey and Monu, 2006). Finally, regulatory T-cell (CD4+, CD25+) induction from within the microenvironment can reduce immune recognition of neoplastic cells, and thus encourage tumor growth (Woo et al., 2001; Sasada et al., 2003; Wang et al., 2006).

In some cancers, fibroblasts constitute a greater proportion of the overall tumor than do the neoplastic cells (Fig. 1). Cancer-associated fibroblasts have been theorized to originate from (1) cancer cells undergoing epithelial-to-mesenchymal transition, (2) marrow-derived cells which have undergone migration to, and activation at, the site of the tumor, and (3) resident fibroblasts which have undergone activation induced by neoplastic cells. Cancer-associated fibroblasts are functionally and phenotypically distinct from normal fibroblasts. Fibroblasts engineered to secrete high levels of hepatocyte growth factor (HGF) or TGF-β initiated cancer at divergent sites, including the stomach and prostate, in rodents (Bhowmick et al., 2004). These findings support the idea that the tumor stroma has a far more complex role than simply serving as a lattice for growth and spread of neoplastic cells. Rather, the interplay between the neoplastic cells and stroma is dynamic, with the tumor-associated fibroblasts playing a key role in the maintenance and progression of the tumor.

Harnessing the immune response

In 1796, Edward Jenner first used the term 'vaccination' to describe his studies which used poxvirus derived from lesions in cows to protect humans against infection with smallpox (Barquet and Domingo, 1997). Later, Louis Pasteur demonstrated that animals and people could be protected against disease when administered microbes that had been attenuated to reduce pathogenicity. From this early work, it became evident that stimulation of the

Please cite this article in press as: Suckow, M.A. Cancer vaccines: Harnessing the potential of anti-tumor immunity. The Veterinary Journal (2013), http://dx.doi.org/10.1016/j.tvjl.2013.06.005

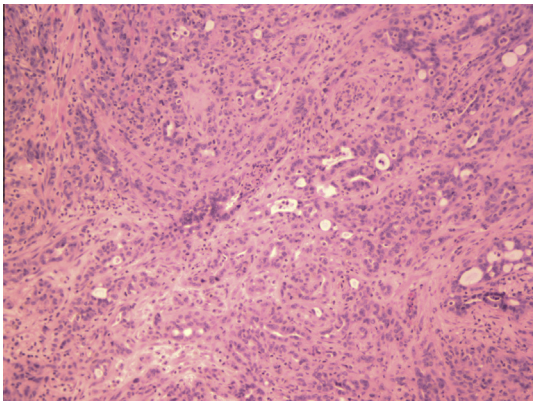

Fig. 1. Photomicrograph of prostate adenocarcinoma from a Lobund-Wistar rat. There is abundant fibrous stroma separating occasional glandular ducts. Stained with hematoxylin and eosin, 400×.

immune system by exposure to specific antigens associated with pathogens could lead to a response that could protect individuals from infection and, of paramount importance, disease associated with infection.

Recent work has extended the use of vaccination as a means to prevent and treat cancer. Vaccines based upon antigens ranging from recombinant subunit proteins to whole, inactivated cancer cells have been evaluated in preclinical models and, in some cases, in clinical trials (Buonaguro et al., 2011; Melenhorst and Barrett, 2011). For example, therapeutic cancer vaccines have been developed which used (1) whole, inactivated autologous or allogeneic cancer cells such as the GVAX vaccine which combines irradiated, cultured cancer cells as a treatment for pancreatic cancer (Lutz et al., 2011); (2) dendritic cells harvested from patients and which undergo in vitro stimulation via pulsing with peptides or proteins have been used to treat prostate cancer, melanoma, and colorectal cancer (Schlom, 2012); (3) peptides or proteins which are either TAAs or proteins associated with a key aspect of tumor progression as vaccine antigens, such as gp100 as an antigen in a therapeutic melanoma vaccine (Schwartzentruber et al., 2011), anti-lymphoma antibody as an antigen in a therapeutic anti-idiotype lymphoma vaccine (Inogés et al., 2011), and cancer testis antigen (CTA) which is sometimes aberrantly expressed on tumor cells and potentially represents an interesting antigen in vaccines for hematologic malignancies (Lim et al., 2012); or (4) delivery of deliver specific antigens to the immune system using recombinant vectors, including Poxvirus to deliver prostate specific antigen (PSA) as a prostate cancer vaccine, *Listeria* to deliver mesothelin as vaccine for pancreatic cancer, and adenovirus to deliver CEA as a vaccine for carcinoma (Schlom, 2012).

One interesting approach that has been tried in rodent models is to use enriched preparations of cancer stem cells obtained directly from tumors as vaccine antigens. Using this approach, Ning et al. (2012) showed that growth of both melanoma and squamous cell carcinoma could be inhibited through vaccination with dendritic cells pulsed with lysates of cancer stem cells and that both cell-mediated and humoral immune responses were activated. Although some approaches to cancer vaccination have shown promise, many more have been limited by the immunosuppressive ability of the tumor and associated stroma.

Therapeutic vaccination for melanoma has been the subject of great effort. Although several vaccine preparations failed in early clinical trials, vaccination with a modified gp100 peptide combined with montanide ISA followed by high-dose IL-2 resulted in generation of melanoma-reactive CTLs in patients with stage IV or locally advanced stage III cutaneous melanoma (Schwartzentruber et al., 2011). Further, progression-free survival was 2.9 months in patients immunized with gp100 and receiving IL-2 versus 1.6 months in those treated with only IL-2. Other studies have shown induction of immune responses following vaccination with combinations of melanoma antigens (Slingluff et al., 2008) and by use of vaccines consisting of patient-specific dendritic cells pulsed with melanoma antigens (Hersey et al., 2004).

Canine malignant melanoma is similar to advanced melanoma in humans, in that both are typically treated initially with aggressive local therapies, including surgery. However, metastatic disease commonly occurs in spite of these efforts. Following diagnosis, dogs generally have median survival times of approximately 12 months from the time of diagnosis (Marino et al., 1995; Spangler and Kass, 2006). A therapeutic melanoma vaccine for dogs has been described which targets tyrosinase, a glycoprotein essential to melanin synthesis. Specifically, the vaccine involves transdermal immunization with xenogeneic human tyrosinase DNA components inserted into a plasmid and induces specific anti-tyrosinase humoral immunity (Bergman, 2007). The ONCEPT vaccine (Merial) was licensed in 2010 by the US Department of Agriculture (USDA) for treatment of dogs with stage II or stage III oral melanoma. As such, ONCEPT is the first plasma DNA-based vaccine on the market for either animals or humans. More recently, studies evaluating the use of murine tryrosinase DNA within a plasmid has been shown to be effective, based on increased survival time, against canine oral melanoma and digital malignant melanoma (Bergman et al., 2006; Manley et al., 2011).

Human prostate cancer is the second leading cause of death related to cancer among men in western countries. Although, surgery or radiation therapy is effective in cases diagnosed early, up to 30% of patients will experience disease recurrence. In 2010, the US Food and Drug Administration (FDA) approved the sipuleucel-T vaccine (Provenge; Dendreon) for the treatment of men with metastatic prostate cancer. The vaccine is prepared from autologous antigen presenting dendritic cells harvested from patient peripheral blood and which are incubated with a recombinant fusion protein composed of prostatic acid phosphatase and GM-CSF. Following incubation, the cells are then infused back to the patient (Kantoff et al., 2010), with treatment being given every 4 weeks for a series of three treatments. Phase III clinical trials demonstrated an overall survival benefit with a 22% reduction in the risk of death and a 4.1 month median survival benefit (Kantoff et al., 2010). In that study, the authors reported that patients treated with sipuleucel-T more frequently experienced adverse events, including chills, fever, and headache.

Cervical cancer results in the deaths of over 250,000 women annually (Arbyn et al., 2011) and requires persistent infection with oncogenic human papillomavirus (HPV), with HPV types 16 and 18 accounting for approximately 70% of invasive cervical cancers worldwide (CDC, 2011). Because prevention of HPV infection equates with protection against development of cervical cancer, prophylactic HPV vaccination is associated with prevention of cervical cancer. Two HPV vaccines are available, one is a quadrivalent vaccine (Gardasil; Merck), and the other is a bivalent vaccine (Cervarix; GlaxoSmithKline). Both vaccines are effective against oncogenic types HPV 16 and 18, and Gardasil is also effective against non-oncogenic types HPV 6 and 11, which cause genital warts. Cervarix and Gardasil are both composed of virus-like particle (VLP) formulations which include HPV components. The Cervarix vaccine also includes as an adjuvant the oil-in-water based emulsion, AS04, while Gardasil includes alum as an adjuvant. Both vaccines induce neutralizing antibody which transudates to the cervical mucosa, the typical site of initial HPV infection (Einstein et al., 2011), although vaccination with Cervarix appeared to induce superior neutralizing antibody levels when compared with Gardasil (Schwarz, 2009).

Because most cancers are complex tissues with an antigenic character that changes as the tumor grows and responds to

Please cite this article in press as: Suckow, M.A. Cancer vaccines: Harnessing the potential of anti-tumor immunity. The Veterinary Journal (2013), http://dx.doi.org/10.1016/j.tvjl.2013.06.005

immunoediting, vaccines which present the immune system with the greatest variety of antigenic targets stand a high chance of eliciting a protective immune response. Though approved cancer vaccines have focused on use of specific DNA and protein molecules as antigens, preclinical data demonstrate the potential utility of tissue vaccines generated using harvested tumor tissue (Suckow et al., 2007). For example, a tissue vaccine produced from harvested tumors was shown to reduce the incidence of autochthonous prostate cancer by 90% (Suckow et al., 2005), to reduce pulmonary metastasis in tumor-bearing rats by 70% (Suckow et al., 2008a), and to augment the efficacy of radiation therapy by over 50% in terms of reduction of tumor size (Suckow et al., 2008b). Further, the efficacy of tissue vaccines was shown to be further enhanced by an extracellular matrix adjuvant that resulted in an additional 60% decrease in tumor size (Suckow et al., 2008c). A key advantage of tissue vaccines is the enormous menu of antigenic targets provided by the harvested tumor tissue, including those expressed by tumor stroma and those which are uniquely expressed during in vivo growth of the tumor.

In general, adverse effects associated with tumor vaccines are relatively mild in comparison to the harsh side-effects of chemotherapy. For example, safety data for the Sipuleucel-T prostate cancer vaccine showed that approximately 5% of patients experienced adverse events including chills, pyrexia, headache, myalgia, influenza-like symptoms, and hyperhidrosis (Hall et al., 2011). Though these relatively mild side-effects pale in comparison to those often experienced by patients undergoing chemotherapy, there may be benefit in some cases to using tumor vaccines as adjuncts to chemotherapy or radiation treatment. For example, use of a vaccine for non-small cell lung cancer, based on the MUC1 antigen, resulted in overall median survival of 53 months when combined with cyclophosphamide vs. 30.6 months in cyclophosphamide-only treated patients having locally advanced stage IIIB disease (Gridelli et al., 2009). Likewise, a tissue vaccine was shown to enhance the anti-tumor effect of fixed-beam irradiation, reducing tumor size by 53% in a rodent model of prostate cancer (Suckow et al., 2008b).

Conclusions

Efforts to understand fully the immune response to cancer are ongoing and robust. Although a great deal has been learned and specific pathways defined, the knowledge base remains incomplete. That cancer might be treated, even prevented, via vaccination is an exciting possibility for a disease that depends upon at least an initial failure of the immune system to remove abnormal cells. It is an important point that veterinary medicine was key in the development and clinical application of the first xenogeneic DNA cancer vaccine. Because many human cancers have veterinary homologues with close clinical behavior, it is reasonable to suggest that cancer immunotherapy is an area where synergy should, and likely will, exist between human and veterinary medicine.

Conflict of interest statement

The author of this paper does not have a financial or personal relationship with other people or organizations that could inappropriately influence or bias the content of this paper.

References

Arbyn, M., Castellsagué, X., de Sanjosé, S., Bruni, L., Saraiya, M., Bray, F., Ferlay, J., 2011. Worldwide burden of cervical cancer in 2008. Annals of Oncology 22, 2675–2686.

Balkwill, F., Charles, K.A., Mantovani, A., 2005. Smoldering and polarized inflammation in the initiation and promotion of malignant disease. Cancer Cell 7, 211–217.

Barquet, N., Domingo, P., 1997. Smallpox: The triumph over the most terrible of the ministers of death. Annals of Internal Medicine 127, 635–642.

Ben-Baruch, A., 2006. Inflammation-associated immune suppression in cancer: The roles played by cytokines, chemokines, and additional mediators. Seminars in Cancer Biology 16, 38–52.

Bennett, W.T., Pandolfi, F., Grove, B.H., Hawes, G.E., Boyle, L.A., Kradin, R.L., Kurnick, J.T., 1992. Dominant rearrangements among human tumor-infiltrating lymphocytes: analysis of T-cells derived from 32 patients with melanoma, lung, and renal cell carcinoma. Cancer 69, 2379–2384.

Bergman, P.J., 2007. Canine oral melanoma. Clinical Techniques in Small Animal Practice 22, 55–60.

Bergman, P.J., Camps-Palau, M.A., McKnight, J.A., Leibman, N.F., Craft, D.M., Leung, C., Liao, J., Rivière, I., Sadelain, M., Hohenhaus, A.E., et al., 2006. Development of a xenogeneic DNA vaccine program for canine malignant melanoma at the Animal Medical Center. Vaccine 24, 4582–4585.

Bhowmick, N.A., Chytil, A., Plieth, D., Gorska, A.E., Dumont, N., Shappell, S., Washington, M.K., Neilson, E.G., Moses, H.L., 2004. TGF-beta signaling in fibroblasts modulates the oncogenic potential of adjacent epithelia. Science 303, 848–851.

Boghossian, S., Robinson, S., Von Delwig, A., Manas, D., White, S., 2011. Immunotherapy for treating metastatic colorectal cancer. Surgical Oncology 21, 67–77.

Briest, F., Berndt, A., Clement, J., Junker, K., Eggeling, F., Grimm, S., Friedrich, K., 2012. Tumor-stroma interactions in tumorigenesis: Lessons from stem cell biology. Frontiers in Bioscience (Elite Edition) 4, 1871–1887.

Buonaguro, L., Petrizzo, A., Tornesello, M.L., Buonaguro, F., 2011. Translating tumor antigens into cancer vaccines. Clinical and Vaccine Immunology 18, 23–34.

Centers for Disease Control and Prevention (CDC), 2011. Progress Toward Implementation of Human Papillomavirus Vaccination – The Americas, 2006–2010. Morbidity and Mortality Weekly Report 60, pp. 1382–1384.

Chow, M.T., Möller, A., Smyth, M.J., 2012. Inflammation and immune surveillance in cancer. Seminars in Cancer Biology 22, 23–32.

Dougan, M., Dranoff, G., 2009. Immune therapy for cancer. Annual Review of Immunology 27, 83–117.

Dranoff, G., 2004. Cytokines in cancer pathogenesis and cancer therapy. Nature Reviews Cancer 4, 11–22.

Dunn, G.P., Bruce, A.T., Ikeda, H., Old, L.J., Schreiber, R.D., 2002. Cancer immunoediting: From immunosurveillance to tumor escape. Nature Immunology 3, 991–998.

Dunn, G.P., Old, L.J., Schreiber, R.D., 2004. The three Es of cancer immunoediting. Annual Review of Immunology 22, 329–360.

Dunn, I.S., Haggerty, T.J., Kono, M., Durda, P.J., Butera, D., Macdonald, D.B., Benson, E.M., Rose, L.B., Kurnick, J.T., 2007. Enhancement of human melanoma antigen expression by IFN-β. Journal of Immunology 179, 2134–2142.

Ehrlich, P., 1909. Ueber den jetzigen stand der Karzinomforschung. Nederlands tijdschrift voor geneeskunde 5, 273–290.

Einstein, M.H., Baron, M., Levin, M.J., Chatterjee, A., Fox, B., Scholar, S., Rosen, J., Chakhtoura, N., Meric, D., Dessy, F.J., et al., 2011. Comparative immunogenicity and safety of human papillomavirus (HPV)-16/18 vaccine and HPV-6/11/16/18 vaccine. Human Vaccines 7, 1343–1358.

Frey, A.B., Monu, N., 2006. Effector-phase tolerance: Another mechanism of how cancer escapes antitumor immune response. Journal of Leukocyte Biology 79, 652–662.

Gajewski, T.F., Meng, Y., Blank, C., Brown, I., Kacha, A., Kline, J., Harlin, H., 2006. Immune resistance orchestrated by the tumor microenvironment. Immunology Reviews 231, 131–145.

Ganss, R., Arnold, B., Hammerling, G.J., 2004. Overcoming tumor-intrinsic resistance to immune effector function. European Journal of Immunology 34, 2635–2641.

Giovannetti, A., Pierdominici, A.Di., Iorio, A., Cianci, R., Murdaca, G., Puppo, F., Pandolfi, F., Paganelli, R., 2008. Apoptosis in the homeostasis of the immune system and in human immune mediated diseases. Current Pharmaceutical Design 14, 253–268.

Goutagny, N., Estornes, Y., Hasan, U., Lebecque, S., Caux, C., 2012. Targeting pattern recognition receptors in cancer immunotherapy. Targeted Oncology 7, 29–54.

Gridelli, C., Rossi, A., Maione, P., Ferrara, M.L., Castaldo, V., Sacco, P.A., 2009. Vaccines for the treatment of non-small cell lung cancer: a renewed anticancer strategy. The Oncologist 14, 909–920.

Groscurth, P., Filgueira, L., 1998. Killing mechanisms of cytotoxic T lymphocytes. News in Physiological Sciences 13, 17–21.

Hall, S.J., Pantuck, A.J., George, D.J., Whitmore, J.B., Frohlich, M.W., Sims, R.B., 2011. Integrated safety data from 4 randomized, double-blind, controlled trials of autologous cellular immunotherapy with sipuleucel-T in patients with prostate cancer. Journal of Urology 186, 877–881.

Hamilton, E., Blackwell, K., Hobeika, A.C., Clay, T.M., Broadwater, G., Ren, X.R., Chen, W., Castro, H., Lehmann, F., Spector, N., et al., 2012. Phase I clinical trial of HER2-specific immunotherapy with concomitant HER2 kinase inhibition. Journal of Translational Medicine 10, 28.

Haslam, S.Z., Woodward, T.L., 2003. Host microenvironment in breast cancer development: epithelial-cell–stromal-cell interactions and steroid hormone action in normal and cancerous mammary gland. Breast Cancer Research 5, 208–215.

Henning, T., Kraus, M., Brischwein, M., Otto, A.M., Wolf, B., 2004. Relevance of tumor microenvironment for progression, therapy and drug development. Anti-Cancer Drugs 15, 7–14.

Hersey, P., Menzies, S.W., Halliday, G.M., Nguyen, T., Farrelly, M.L., DeSilva, C., Lett, M., 2004. Phase I/II study of treatment with dendritic cell vaccines in patients with disseminated melanoma. Cancer Immunology Immunotherapy 53, 125–134.

Please cite this article in press as: Suckow, M.A. Cancer vaccines: Harnessing the potential of anti-tumor immunity. The Veterinary Journal (2013), http://dx.doi.org/10.1016/j.tvjl.2013.06.005

Hishii, M., Andrews, D., Boyle, L.A., Wong, J.T., Pandolfi, F., van den Elsen, P.J., Kurnick, J.T., 1997. In vivo accumulation of the same anti-melanoma T cell clone in two different metastatic sites. Proceedings of the National Academy of Sciences of the United States of America 94, 1378–1383.

Huang, B., Zhao, J., Li, H., He, K.L., Chen, Y., Chen, S.H., Mayer, L., Unkeless, J.C., Xiong, H., 2005. Toll-like receptors on tumor cells facilitate evasion of immune surveillance. Cancer Research 66, 5009–5014.

Inogés, S., de Cerio, A.L., Villanueva, H., Soria, E., Pastor, F., Bendandi, M., 2011. Idiotype vaccines for lymphoma therapy. Expert Review of Vaccines 10, 801–809.

Iwasaki, A., Medzhitov, R., 2004. Toll-like receptor control of the adaptive immune responses. Nature Immunology 5, 987–995.

Kantoff, P.W., Higano, C.S., Shore, N.D., Berger, E.R., Small, E.J., Penson, D.F., Redfern, C.H., Ferrari, A.C., Dreicer, R., Sims, R.B., Xu, Y., Frohlich, M.W., Schellhammer, P.F., 2010. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. New England Journal of Medicine 363, 411–422.

Kelly, M.G., Alvero, A.B., Chen, R., Silasi, D.A., Abrahams, V.M., Chan, S., Visintin, I., Rutherford, T., Mor, G., 2006. TLR-4 signaling promotes tumor growth and paclitaxel chemoresistance in ovarian cancer. Cancer Research 66, 3859–3868.

Lim, S.H., Zhang, Y., Zhang, J., 2012. Cancer-testis antigens: The current status on antigen regulation and potential clinical use. American Journal of Blood Research 2, 29–35.

Lu, H., Goodell, V., Disis, M., 2008. Humoral immunity directed against tumor-associated antigens as potential biomarkers for the early diagnosis of cancer. Journal of Proteome Research 7, 1388–1394.

Lutz, E., Yeo, C.J., Lillemoe, K.D., Biedrzycki, B., Kobrin, B., Herman, J., Sugar, E., Piantadosi, S., Cameron, J.L., Solt, S., et al., 2011. A lethally irradiated allogeneic granulocyte-macrophage colony stimulating factor-secreting tumor vaccine for pancreatic adenocarcinoma. A Phase II trial of safety, efficacy, and immune activation. Annals of Surgery 253, 328–335.

Manley, C.A., Leibman, N.F., Wolchok, J.D., Rivière, I.C., Bartido, S., Craft, D.M., Bergman, P.J., 2011. Xenogeneic murine tyrosinase DNA vaccine for malignant melanoma of the digit of dogs. Journal of Veterinary Internal Medicine 25, 94–99.

Mantovani, A., Cassatella, M.A., Costantini, C., Jaillon, S., 2011. Neutrophils in the activation and regulation of innate and adaptive immunity. Nature Reviews Immunology 11, 519–531.

Marino, D.J., Matthiesen, D.T., Stefanacci, J.D., Moroff, S.D., 1995. Evaluation of dogs with digit masses: 117 cases (1981–1991). Journal of the American Veterinary Medical Association 207, 726–728.

Mazurek, U., Owczarek, A., Nowakowska-Zajdel, E., Wierzgon, J., Grochowska-Niedworok, E., Kokot, T., Muc-Wierzgon, M., 2011. Statistical analysis of differential gene expression in colorectal cancer using clear-test. Journal of Biological Regulators and Homeostatic Agents 25, 279–283.

Melenhorst, J.J., Barrett, A.L., 2011. Tumor vaccines and beyond. Cytotherapy 13, 8–18.

Meulmeester, E., ten Dijke, P., 2011. The dynamic roles of TGF-β in cancer. Journal of Pathology 223, 205–218.

Ning, N., Pan, Q., Zheng, F., Teitz-Tennenbaum, S., Egenti, M., Yet, J., Li, M., Ginestier, C., Wicha, M.S., Moyer, J.S., et al., 2012. Cancer stem cell vaccination confers significant antitumor immunity. Cancer Research 72, 1853–1864.

Onizuka, S., Tawara, I., Shimizu, J., Sakaguchi, S., Fujita, T., Nakayama, E., 1999. Tumor rejection by in vivo administration of anti-CD25 (interleukin-2 receptor) monoclonal antibody. Cancer Research 59, 3128–3133.

Ostrand-Rosenberg, S., Sinha, P., 2009. Myeloid-derived suppressor cells: Linking inflammation and cancer. Journal of Immunology 182, 4499–4506.

Palma, G., De Laurenzi, V., De Marco, M., Barbieri, A., Petrillo, A., Turco, M.C., Arra, C., 2012. Plasmacytoids dendritic cells are a therapeutic target in anticancer immunity. Biochimica et Biophysica Acta 1826, 407–414.

Pandolfi, F., Cianci, R., Lolli, S., Dunn, I.S., Newton, E.E., Haggerty, T.J., Boyle, L.A., Kurnick, J.T., 2008. Strategies to overcome obstacles to successful immunotherapy of melanoma. International Journal of Immunopathology and Pharmacology 21, 493–500.

Perdrizet, G.A., Ross, S.R., Stauss, H.J., Singh, S., Koeppen, H., Schreiber, H., 1990. Animals bearing malignant grafts reject normal grafts that express through gene transfer the same antigen. Journal of Experimental Medicine 171, 1205–1220.

Placke, T., Salih, H.R., Kopp, H.-G., 2012. GITR ligand provided by thromobopoietic cells Inhibits NK cell antitumor activity. The Journal of Immunology 189, 154–160.

Räsänen, K., Vaheri, A., 2010. Activation of fibroblasts in cancer stroma. Experimental Cell Research 316, 2713–2722.

Reed, J.C., 1999. Mechanisms of apoptosis avoidance in cancer. Current Opinion in Oncology 11, 68–75.

Rippo, M.R., Villanova, F., Tomassoni Ardori, F., Graciotti, L., Amatori, S., Manzotti, S., Fanelli, M., Gigante, A., Procopio, A., 2010. Dexamethasone affects Fas- and serum deprivation-induced cell death of human osteoblastic cells through surviving regulation. International Journal of Immunopathology and Pharmacology 23, 1153–1165.

Sasada, T., Kimura, M., Yoshida, Y., Kanai, M., Takabayashi, A., 2003. CD4+CD25+ regulatory T cells in patients with gastrointestinal malignancies: Possible involvement of regulatory T cells in disease progression. Cancer 98, 1089–1099.

Schlom, J., 2012. Therapeutic cancer vaccines: Current status and moving forward. Journal of the National Cancer Institute 104, 599–613.

Schor, S.L., Scor, A.M., 2001. Phenotypic and genetic alterations in mammary stroma: Implications for tumour progression. Breast Cancer Research 3, 373–379.

Schwartzentruber, D.J., Lawson, D.H., Richards, J.M., Conry, R.M., Miller, D.M., Treisman, J., Gailani, F., Riley, L., Conlon, K., Pockaj, B., et al., 2011. Gp100 peptide vaccine and interleukin-2 in patients with advanced melanoma. New England Journal of Medicine 364, 2119–2127.

Schwarz, T.F., 2009. Clinical update of the AS04-advuvanted human papillomavirus-16/18 cervical cancer vaccine, Cervarix®. Advances in Therapy 26, 983–998.

Shekhar, M.P., Werdell, J., Santner, S.J., Pauley, R.J., Tait, L., 2001. Breast stroma plays a dominant regulatory role in breast epithelial growth and differentiation: Implications for tumor development and progression. Cancer Research 61, 1320–1326.

Shimizu, J., Yamazaki, S., Sakaguchi, S., 1999. Induction of tumor immunity by removing $CD25^+$ $CD4^+$ T cells: A common basis between tumor immunity and autoimmunity. Journal of Immunology 163, 5211–5218.

Silze, T., Randolph, G.J., Kreutz, M., Kunz-Schughart, L.A., 2004. The fibroblast: Sentinel cell and local immune modulator in tumor tissue. International Journal of Cancer 108, 173–180.

Sims, G.P., Rowe, D.C., Rietdijk, S.T., Herbst, R., Coyle, A.J., 2009. HMGB1 and RAGE in inflammation and cancer. Annual Review of Immunology 28, 367–388.

Singh, S., Ross, S.R., Acena, M., Rowley, D.A., Schreiber, H., 1992. Stroma is critical for preventing or permitting immunological destruction of antigenic cancer cells. Journal of Experimental Medicine 175, 139–146.

Slingluff Jr., C.L., Petroni, G.R., Olson, W., Czarkowski, A., Grosh, W.W., Smolkin, M., Chianese-Bullock, K.A., Neese, P.Y., Deacon, D.H., Nail, C., et al., 2008. Helper T-cell responses and clinical activity of a melanoma vaccine with multiple peptides from MAGE and melanocytic differentiation antigens. Journal of Clinical Oncology 26, 4973–4980.

Spangler, W.L., Kass, P.H., 2006. The histologic and epidemiologic bases for prognostic considerations in canine melanocytic neoplasia. Veterinary Pathology 43, 136–149.

Suckow, M.A., Wolter, W.R., Pollard, M., 2005. Prevention of de novo prostate cancer by immunization with tumor-derived vaccines. Cancer Immunology Immunotherapy 54, 571–576.

Suckow, M.A., Heinrich, J., Rosen, E.D., 2007. Tissue vaccines for cancer. Expert Review of Vaccines 6, 925–937.

Suckow, M.A., Wolter, W.R., Sailes, V.T., 2008a. Inhibition of prostate cancer metastasis by administration of a tissue vaccine. Clinical and Experimental Metastasis 25, 913–918.

Suckow, M.A., Wheeler, J., Wolter, W.R., Sailes, V., Yan, M., 2008b. Immunization with a tissue vaccine enhances the effect of irradiation on prostate tumors. In Vivo 22, 171–178.

Suckow, M.A., Hall, P., Wolter, W., Sailes, V., Hiles, M.C., 2008c. Use of an extracellular matrix material as a vaccine carrier and adjuvant. Anticancer Research 28, 2529–2534.

Swann, J.B., Smyth, M.J., 2007. Immune surveillance of tumors. Journal of Clinical Investigation 117, 1137–1146.

Szczepanski, M.J., Czystowska, M., Szajnik, M., Harasymczuk, M., Boyiadzis, M., Kruk-Zagajewska, A., Szyfter, W., Zeromski, J., Whiteside, T.L., 2009. Triggering of Toll-like receptor 4 expressed on human head and neck squamous cell carcinoma promotes tumor development and protects the tumor from immune attack. Cancer Research 69, 3105–3113.

Wang, Y., Zhou, L., Wang, H.Y., Xiao, J.X., Si, L.S., Wang, Y.L., 2006. The ex vivo microenviroments in MLTC of poorly immunogenic tumor cells facilitate polarization of CD4+CD25+ regulatory T cells. Cellular & Molecular Immunology 3, 123–129.

Whiteside, T.L., 2006. Immune suppression in cancer: Effects on immune cells, mechanism and future therapeutic intervention. Seminars in Cancer Biology 16, 3–15.

Woo, E.Y., Chu, C.S., Goletz, T.J., Schlienger, K., Yeh, H., Coukos, G., Rubin, S.C., Kaiser, L.R., June, C.H., 2001. Regulatory CD4(+)CD25(+) T cells in tumors from patients with early-stage non-small cell lung cancer and late-stage ovarian cancer. Cancer Research 61, 4766–4772.

Yee, C., Thompson, J.A., Byrd, D., Riddell, S.R., Roche, P., Celis, E., Greenberg, P.D., 2002. Adoptive T cell therapy using antigenspecific CD[8] T cell clones for the treatment of patients with metastatic melanoma: In vivo persistence, migration, and antitumor effect of transferred T cells. Proceedings of the National Academy of Science of the United States of America 99, 16168–16173.

Zou, W., 2006. Regulatory T cells, tumour immunity and immunotherapy. Nature Reviews Immunology 6, 295–307.

Please cite this article in press as: Suckow, M.A. Cancer vaccines: Harnessing the potential of anti-tumor immunity. The Veterinary Journal (2013), http://dx.doi.org/10.1016/j.tvjl.2013.06.005