Immunosuppressive networks and checkpoints controlling antitumor immunity and their blockade in the development of cancer immunotherapeutics and vaccines

A Q Butt and K H G Mills

Oncogene (2014) 33, 4623–4631; doi:10.1038/onc.2013.432; published online 21 October 2013

Vaccines that promote protective adaptive immune responses have been successfully developed against a range of infectious diseases, and these are normally administered prior to exposure with the relevant virus or bacteria. Adaptive immunity also plays a critical role in the control of tumors. Immunotherapeutics and vaccines that promote effector T cell responses have the potential to eliminate tumors when used in a therapeutic setting. However, the induction of protective antitumor immunity is compromised by innate immunosuppressive mechanisms and regulatory cells that often dominate the tumor microenvironment. Recent studies have shown that blocking these suppressor cells and immune checkpoints to allow induction of antitumor immunity is a successful immunotherapeutic modality for the treatment of cancer. Furthermore, stimulation of innate and consequently adaptive immune responses with concomitant inhibition of immune suppression, especially that mediated by regulatory T (Treg) cells, is emerging as a promising approach to enhance the efficacy of therapeutic vaccines against cancer. This review describes the immunosuppressive mechanisms controlling antitumor immunity and the novel strategies being employed to design effective immunotherapeutics against tumors based on inhibition of suppressor cells or blockade of immune checkpoints to allow induction of more potent effector T cell responses. This review also discusses the potential of using a combination of adjuvants with inhibition of immune checkpoint or suppressor cells for therapeutic vaccines and the translation of preclinical studies to the next-generation vaccines against cancer in humans. Keywords: immunotherapy; vaccine; antitumor immunity; immune checkpoint; regulatory T cell; Toll-like receptor agonist

INTRODUCTION

It is well established that the immune system can restrain tumor growth. Adaptive immune responses, in particular IFN-γ-secreting T cells, play a central role in tumor immune surveillance. However, tumor growth is also associated with immune escape, immune subversion and immune suppression. Immunoediting gives rise to tumor variants that can escape immune surveillance.

Immune suppression strategies include downregulation of MHC class I or co-inhibitory molecules, such as CD80/86 on antigen-presenting cells (APC) or enhancement of co-inhibitory inhibitory molecules such as cytotoxic T lymphocyte antigen 4 (CTLA-4) or programmed death-1 (PD-1) on T cells. Furthermore, the development of cancer is associated with the induction or recruitment of regulatory cells and the production of molecules that suppress antitumor effector T cell responses. These immune suppression networks include regulatory T (Treg) cells, myeloid derived suppressor cells (MDSC) and type 2 (M2) macrophages, as well as the immunosuppressive cytokines, IL-10 and TGF-β.

The potential of using immunotherapy, where the patient’s own immune system is enhanced to attack tumors, is gaining momentum as a viable approach for the treatment of cancer. Immunotherapeutic approaches include strategies that directly enhance antitumor immunity or that block immune checkpoints or suppressor networks, thus allowing the development of effector immune responses that eliminate the tumor (Figure 1). Immune-activating approaches include nonspecific stimulation of innate or adaptive immune responses against the tumor or specific stimulation of tumor-specific immune responses using vaccines that include tumor antigens. The aim is to selectively promote effective cytotoxic T lymphocyte (CTL) and Th1 responses against the tumor.

Prophylactic vaccines against infectious disease are among the most effective and least expensive interventions in modern medicine and function by generating protective adaptive immune responses with the help of adjuvants that activate innate immune responses. However, the application of these approaches against cancer is still in its infancy and is compromised by the fact that they must break tolerance to self-antigens, they must work therapeutically and they must overcome the immunosuppressive environment of the growing tumor.

Dendritic cells (DCs) are key antigen APC, which play a vital role in activating and directing adaptive immune responses and thus DCs are being exploited in the development of vaccines against a range of cancers. The first licensed DC-based cancer vaccine Provenge® induces antitumor responses in vivo by the adoptive transfer of DCs pulsed in vitro with tumor antigens and stimulated to mature with cytokines and immunomodulatory molecules. Nevertheless, this DC-based tumor vaccine confers only modest survival advantage and has limited success in mediating tumor regression.
Figure 1. The pro- and anti-tumor arms of the immune response and the targets for the development of cancer immunotherapeutics and vaccines. The induction of antitumor immunity is dependent on activating DCs to express costimulatory molecules and innate inflammatory cytokines such as IL-12, IL-23, and IL-1 that promote Th1 and CTL responses. T cells secrete IFN-γ, TNF-α, and IL-17, which have antitumor effects. However, these effector responses are suppressed by co-inhibitory molecules, such as PD-1/PD-L1, CTLA-4 and expansion of regulatory DCs (DCI), M2 macrophages and MDSC. These innate suppressor cells secrete IL-10 and TGF-β, which together with retinoic acid (RA) enhance induction of Treg cells that are recruited to the tumor under the influence of the chemokines, including CCL22 and OX40L. Treg cells and innate suppressor cells suppress effector immune responses and thereby promote the growth of tumors. TLR agonists, such as or and vaccines promote innate and adaptive immune responses, while cell-based therapies with DCs or T cells can also enhance antitumor immunity. Conversely, or in combination with these immune activating strategies, antibodies can block cytokines of the suppressive pathways and molecules can block immune checkpoints and suppressor cells and thereby enhance antitumor immunity. DC, dendritic cell; TLR, Toll-like receptor; αGalCer, α-galactosylceramide; mAb, monoclonal antibody; IL-12, IL-23; OX40, OX40 ligand; PD-L1, PD-L2; TGF-β, transforming growth factor-β; Treg, regulatory T cell; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; NKG2D, natural killer cell lectin-like receptor; CD4, cluster of differentiation 4; PD-1, programmed cell death protein 1; KAP, killer cell immunoglobulin-like receptor; p38, MAP kinase inhibitor; RAL, retinoic acid receptor-alpha inhibitor.

Toll-like receptor (TLR) agonists are potent activators of innate immune cells and also direct adaptive immunity and thus have been employed as adjuvants in a number of experimental cancer vaccines and have been tested in clinical trials. Although the TLR agonist, imiquimod, is being used in humans for the treatment of superficial basal cell carcinoma, clinical trials with other TLR agonists have not been so effective. One reason for their relatively modest success with TLR agonist-based immunotherapies and vaccines is that TLR agonists can promote regulatory as well as effector T cell responses and this is compounded in a therapeutic setting by the high prevalence of Treg cells infiltrating the tumor.

The selection of Treg cells can be used as an indicator of tumor response in vivo in mouse tumor models. Furthermore, ipilimumab, a monoclonal neutralizing antibody that blocks CTLA-4, has shown good results in melanoma patients, has been approved by the FDA. Another therapeutic monoclonal antibody, mAbs targeting the anti-costimulatory protein B7-H1 (PD-L1), is being developed for the treatment of melanoma, renal cell carcinoma, and non-small cell lung cancer. However, persistent blockade of these inhibitory receptors can have lead to the breakdown in immune self-tolerance, thereby increasing susceptibility to autoimmune or auto-inflammatory side effects, including rash, colitis, hepatitis and endocrinopathies. Alternatively, cancer vaccines that are rationally designed to specifically block tumor-associated immune checkpoints may have reduced side effects. These could potentially involve combination therapy approaches, including inhibition of immunosuppressive cells, blockade of co-inhibitory molecules and the simultaneous activation of immune signaling pathways via TLR agonists to promote effector immune responses.

TARGETING TUMOR INfiltrating IMMUNOSupPRESSIVE CELLS

The induction of effective antitumor immune responses is hindered by the high number of infiltrating immunosuppressive cells. In the tumor micro-environment, which in turn leads to poor effector immune responses. Therefore, targeting immunosuppressive cells, including Treg cells, MDSC and M2 macrophages has emerged as a leading approach to the development of new immunotherapeutics and vaccines against cancer.

Regulatory T cells play a crucial role in maintaining the immune homeostasis, which depends on the balance between the immune responses that control infectious pathogens and tumors and the reciprocal immune responses that prevent inflammation and autoimmune diseases. It is now well recognized that the natural Treg cells expressing FOXP3 and inducible antigen-specific Treg cells that secrete IL-10 and TGF-beta play a protective role in immunity to infection by controlling pathogen-induced immunopathology and also prevent the development of autoimmune disease. However, in the tumor environment the frequency of Treg cells versus effector T cells is greater than in the general circulation, and their recruitment and activation is associated with tumor growth because of the local inhibition of the effector immune responses. Therefore, depletion of Treg cells can enhance the development of protective T cell responses and induction of antitumor immunity. Indeed, the effective immunosuppressive effects of Treg cells may in part explain the failure of many immunotherapeutic approaches to cancer. The inhibition of immunosuppressive cells using cyclosporin A treatment has been shown to enhance antitumor immunity induced by vaccination in melanoma and pancreatic cancer patients. Furthermore, adoptive transfer of regulatory T cells can deplete effector cells that mediate antitumor immunity. However, it is now accepted that more precise strategies are required to inhibit Treg cells to enhance effector cells that mediate antitumor immunity.

Treg cell depletion strategies have utilized monoclonal neutralizing antibodies or ligand-directed toxins targeted to cell surface receptors, such as CD55. Two anti-CD25 antibodies, daclizumab and basiliximab induce Treg cell death by cytokine deprivation (IL-2) and by triggering antibody-dependent, cell-mediated cytotoxicity or complement-mediated cytotoxicity. The results of clinical trials have shown that daclizumab depletes Treg cells and thereby enhances CTL responses to tumor antigens induced by vaccination without any autoimmune side effects. In addition to Treg cell depletion, a new approach to improve antitumor immunity has been utilized to eliminate the immunosuppressive effects of Treg cells in solid tumors. For example, a transgenic mouse with a transgenic Treg cell that expresses a transgenic Treg cell that expresses an anergic tumor cell, the glucocorticoid-induced tumor necrosis factor receptor (GITR) receptor, which is constitutively expressed on Treg cells, was also involved in the antitumor immunity and eradicated established tumors in mice. Another strategy induces the proliferation of Treg cells to the TH2 cytokine signaling using an anti-CD25 ligand (RANKL) antibody denosumab, which blocks the engagement of RANKL on Treg cells to the RANK receptor on the tumor cells and thus blocks Treg cell-induced metastases of tumors in mice. Furthermore, targeting the Treg cell transcription factor FOXP3 by RNA interference, such as miR-31 (negative regulator of FOXP3), can modulate Treg cell functionality and ablates their suppressor activity.
Furthermore, a peptide inhibitor of FOXP3 has been shown to impair Treg cell activity and enhance the efficacy of peptide vaccine against CT-26 tumors in mice. However, translating these approaches to clinical applications will be challenging, as they would have to be specifically delivered to tumor infiltrating Treg cells in secondary lymphoid organs in activated effector T cells and in certain cancer cells.

Despite the obvious benefits of increasing effector T cells in the tumor environment, depletion of Treg cells may also have a high risk of developing systemic autoimmune diseases due to increased inflammatory responses. Thus, alternative approaches need to be developed that involve selective inhibition of regulatory cells. Immune suppressive cells in the tumor with optimal activation of antitumor T cell responses. One approach may be to target Treg cell migration into tumor. Studies in cancer patients have demonstrated significant trafficking of Tregs into tumors and have found an association between the frequency of intratumoral Treg cells and poor survival. Tumor cells and macrophages produce the chemokine CCL2 which promotes trafficking of Treg cells that express CD90, the receptor for CCL2. Studies in mice showed that in vivo blockade of CCL2 reduced the trafficking of Treg cells into tumors. 

M2 macrophages

M2 macrophages are a dominant population of immune cells present in the tumor microenvironment and are most characterized by alternatively-activated M1-like macrophages, which are anti-inflammatory, immunosuppressive and facilitate tumor progression. Unlike M1 macrophages, which are highly inflammatory, microbicidal and tumoricidal, M2 macrophages play a significant role in promoting tumor growth, angiogenesis, metastasis, matrix remodeling and facilitate immune evasion in various human and animal models. M2 macrophages also provide chemoattractant signals, 

Myeloid-derived suppressor cells

MDSs are another class of immune suppressive cells, which are a heterogeneous population of immature myeloid cells that accumulate in conditions of inflammation and in tumors and exert inhibitory function on immune responses. MDSs are thought to promote the tumor growth by both enhancing tumor angiogenesis and by escape from antitumor effector T cell responses. Under normal physiological conditions, these cells are generated in bone marrow and differentiate into mature macrophages, DCs and granulocytes. However, in pathological conditions, there is a dramatic expansion of these Gr1+CD11b+ cells, with the same phenotype and immunosuppressive activity in various tissues, and the differentiation into mature myeloid cells is blocked. MDSs regulate innate immune and T cell responses by depleting antitumor:Modulating cytokine production by macrophages, unregulating the production of immune-suppressive factors, such as nitric oxide and reactive oxygen species, and by overexpressing anti-inflammatory cytokines, such as TGF-β and IL-10. MDSs suppress proliferation and cytokine production by T cells and natural killer cells, as well as induce apoptosis of CD8+ T cells.

Interestingly, MDSs have also been shown to indirectly suppress T cell activation by inducing other immunosuppressive cells such as Treg cells and M2 macrophages. The MDS accumulation in the immunosuppressive pathogenic setting suggests that increased MDS numbers play a protective role by providing an immunosuppressive factor for the maintenance of homeostasis. In the tumor environment, the anti-inflammatory effect of MDSs leads to attenuation of antitumor immunity. Thus, targeting the inhibitory functions of MDSs present a promising approach to enhance therapeutic potential of antitumor vaccines and immunotherapies.

And-Gm monoclonal antibodies have been widely used to deplete MDSs in vivo in mice. However, the clinical translation of anti-Gm antibodies to deplete MDSs in humans is challenging, since they recognize both Ly6G and Ly6C (molecules that express the Gr1 epitope on MDS), which could lead to non-selective depletion of monocytes, T cells, natural killer cells and macrophages and might impair host immunity and lead to opportunistic infections. Recently, preclinical and clinical studies have shown that targeting the differentiation of immature suppressive MDSs into mature, non-suppressive cells such as myeloid DCs, CD4+ and CD8+ T cells using anti-retroinhibitor antibodies and Vitamin D3 can enhance the antitumor immune responses. A number of strategies have been used to deplete MDSs, including the use of chemotherapeutic drug gemcitabine, the sunsold, etc. MDSs have also been shown to inhibit the suppressive function MDCS whereas restore T cell proliferation and decrease tumor growth in vivo. These MDSs depletion and inhibitory approaches can improve immune surveillance and promote antigen-specific responses, thus targeting MDSs may be a promising approach for enhancing the efficacy of cancer vaccines or immunotherapies.

BLOCKADE OF IMMUNE CHECKPOINTS

Among the most promising approaches to stimulate therapeutic antitumor immunity is the blockade of the immune checkpoints. Immune checkpoints are inhibitory pathways employed by the immune system to maintain self-tolerance and thereby prevent the development of autoimmunity. They also help to regulate the duration and amplitude of physiological immune responses against pathogens in order to minimize collateral tissue damage and prevent immunopathology during infection. There is increasing evidence that tumors exploit certain immune checkpoint pathways and thereby subvert antitumor immunity, especially T cell responses specific for tumor antigens. Fortunately, most of the immune checkpoint pathways are initiated by ligand-receptor
interactions, thus they can be readily blocked using neutralizing monoclonal antibodies and inhibitory peptides or modulated using receptor antagonists. This can help to drive effector immune responses and can enhance the efficacy of vaccine and immunotherapeutics.

The APC interaction involves cell surface co-stimulatory and co-inhibitory molecules, as well as membrane receptors that are involved in adhesion and migration. These include members of the immunoglobulin superfamily, such as CD80/CD86, CD40, and the TNF receptor (TNFR) superfamily, such as CD40/CD40L. Antagonizing the interaction between co-inhibitory cell surface receptors with neutralizing antibodies or inhibitory peptides can block the tolerogenic pathways. For example, blockade of CTLA-4 pathway and programmed cell death protein 1 (PD-1)-PD-L1 (also known as B7 homolog 1; B7H1) pathway can enhance immune responses. DCs from ovarian carcinomas overexpress B7-H1 (PD-1) and blockade of B7-H1 reduced IL-10 and enhanced IFN-γ production by T cells, thereby reduced the growth of human ovarian carcinoma in non-obese diabetic/severe combined immunodeficient mice. Furthermore, B7-H4 expression in gastric cancer is associated with poor survival. Expression of B7-H4 by APC is enhanced by Treg cells through IL-10 production, and blockade of B7-H4 enhances antitumor T cell responses. Alternatively, agonists that induce signaling via co-stimulatory cell surface receptors, such as CD28, CD152, CD27 and CD40 have been used to enhance lymphocyte priming to promote antitumor immune responses.

Ipilimumab, a CTLA-4-specific monoclonal antibody, developed by Bristol Myers Squibb, has been approved by the FDA in 2011 for the treatment of metastatic melanoma, including immune-based therapy on the blockade of immune checkpoints. However, the activation of CTLA-4 is associated with immune-related adverse events, including colitis/diarrhea, dermatitis, hepatitis and endocrinopathies. Another CTLA-4-specific monoclonal antibody, tremelimumab, is currently being evaluated for the treatment of several other cancers as a monotherapy, or as an adjuvant in a DC vaccine.

An antibody that targets the co-inhibitory molecule PD-3, BMS 936558, has been evaluated in clinical trials and has shown significant and durable responses in several types of refractory tumors. This antibody was designed to reverse the generation of immunomodulatory cytokines that stimulate highly effective and long-lasting host tumor immunity with controllable autoimmune reactions. However, colorectal toxicities have been reported with this antibody. Other drugs that target PD-1, including M34875, CT-011 and ANP-224 are currently in clinical trials for different cancers. Furthermore, GSK, AstraZenica and Roche have antibodies against PD-L1 under clinical evaluation for solid tumors, melanoma or renal cell cancer.

Additional immune checkpoint inhibitors under evaluation include those that target lymphocyte activation gene 3 (LAG-3), B7-H4 (also known as CD244), 8 and 9, and T lymphocyte activation, T cell membrane proteins B7-H4, and adenosine A2A receptors.

A number of immunotherapeutics based on multiple antibody and immunoglobulin fusion proteins targeting co-inhibitory molecules are in preclinical and clinical trials (for example, IM321 against lymphocyte activation gene 3 is in phase III clinical trial in breast cancer). Alternatively, the direct activation of co-stimulatory molecule signaling pathways using agonists, such as the monoclonal antibody TRN142 specific for CD28 has the capacity to stimulate naive human T cells without the need for a T cell receptor signal. This has been evaluated in clinical trials. However, within 90 min of infusion of the antibody, severe systemic inflammatory responses were induced, characterized by a massive pro-inflammatory cytokine storm followed by multi-organ injury and lymphocyte depletion. Fortunately, all volunteers survived after receiving immunosuppressive treatments and cardiopulmonary support, and this trial cautioned against the global non-discriminatory stimulation of naive T cell activation.

**TLR Ligands as Immunotherapeutics and Adjuvants for Cancer Vaccines**

A new approach to the development of tumor vaccines and immunotherapies has been focused on harnessing the efficacy of targeting immune cells and the receptors that mediate their activation. These recognition receptors, in particular TLRs, sense pathogen-associated molecular patterns and are the primary targets for activation of the innate immune cells and are fundamental in the development of effective adaptive immune responses. Innate immune cells not only act as APCs for T cells but also provide signals necessary for T cell activation. Ligand binding to the TLRs, such as lipopolysaccharide to TLR4, flagellin to TLR5, CpG to TLR9, activates downstream intracellular signaling cascades through the transcription factors NF-κB, interferon regulatory factor 3, mitogen-activated protein kinases leading to the production of pro-inflammatory cytokines and type I interferons, which in turn activate co-stimulatory molecules, which are necessary for the antigen-presenting function of DCs and macrophages to activate T cells. Therefore, TLR agonists are potent activators of innate and adaptive immune responses and thus can act as adjuvants to promote immune responses against tumor antigens.

Synthetic ligands for TLR4, TLR5 and TLR9 have been through clinical trials against cancer and the TLR7 agonist, Imiquimod (Aldecid) has been licensed for clinical use for the treatment of superficial basal cell carcinoma. However, unsatisfactory results have been obtained from clinical trials with other TLR agonists, and one pharmaceutical company halted its clinical program for PSS-312676, a CpG oligodeoxynucleotide that activates TLR9. Furthermore, the TLR8 agonists OX-432 and OX-P8A have been evaluated as immunotherapeutics for uterine, cervical and non-small lung cancer, but did not show promising results in most patients.

In addition to the use of TLR agonists as direct tumor immunotherapeutics, TLR agonists have also been used as adjuvants for co-administration with tumor antigens, recombinant proteins or killed tumor cells. This approach is based on the premise that tumor cells and their products can activate innate immune cells and induce cytokine responses that are capable of eliciting tumor-specific immune responses. A study of tigilus administered with a tumor lysate-pulsed DC vaccine is also ongoing in patients with malignant glioma. Immune responses in melanoma patients with Melan-A/MART1 peptide formulated in incomplete Freund's adjuvant with CpG-GD1 induced strong antigen-specific CD8 T cell responses.

Studies in mice have demonstrated mixed results with TLR agonists as adjuvants for tumor vaccines. Prophylactic but not therapeutic immunization with CpG-GD1 in a transgenic mouse model expressing SV40 T Ag prevented tumor growth. Furthermore, immunization of Tg mice expressing the Her-2/neu gene product with a synthetic peptide specific for Her-2/neu in combination with CpG-GD1 prevented tumor growth in mice. Furthermore, the efficacy of a DC vaccine was enhanced with the use of CpG as an adjuvant in the presence of a p38 mitogen-activated protein kinases signaling inhibitors. Finally, the therapeutic efficacy of adenovirus expressing human cytotoxic-related protein 2 was enhanced with a peritumoral injection of CpG and poly(I:C) (a synthetic ligand for TLR3).

It has also been demonstrated that TLR agonists have the potential to break tolerance to self-antigens by inhibiting the
function of immunosuppressive cells such as Tregs.\textsuperscript{129-131} TLR-induced IL-6 production by DCs blocked the suppressive function of CD4\textsuperscript{+}CD25\textsuperscript{+} Treg cells.\textsuperscript{129} The TLR3 agonist Poly(I:C) has been shown to enhance tumor-suppressing M1 macrophages and thus inhibit the production of anti-inflammatory cytokines IL-10 and TGF-\beta.\textsuperscript{132,133} Furthermore, lipopolysaccharide and Cpg can enhance activation of NF-\kappaB pathways important for the establishment of the M1 phenotype of macrophages and their production of the inflammatory cytokines IL-12, IFN-\gamma, and TNF-\alpha.\textsuperscript{134,135} It is now recognized that TLR agonists are effective adjuvants for cancer vaccines through their ability to promote the differentiation of IFN-\gamma-secreting Th1 cells. However, TLR2 agonists have the potential to inhibit effector T cell responses\textsuperscript{136} and all TLR agonists stimulate IL-10 as well as IL-12 production from DC and thereby promote induction of IL-10 Treg as well as Th1 cells.\textsuperscript{137} This has led to the idea of using combinations of TLR activation with inhibitors of Treg cell induction to promote more effective antitumor immunity.\textsuperscript{137}

COMBINATION STRATEGIES FOR NEXT-GENERATION CANCER IMMUNOTHERAPEUTICS AND VACCINES

Our increased understanding of the tumor microenvironment and the immune responses that mediate and regulate antitumor immunity has provided a foundation for the rational development of vaccines and Immunotherapeutic approaches for the treatment of cancer. Whilst vaccines and immunotherapeutics that target one arm of the immune system have shown some promising results in generating antitumor responses, many of these are subverted by a failure to block the regulatory responses associated with the tumor. Conversely, strategies that globally suppress Treg cells increase the risks for the patient of developing autoimmune diseases. The design of combination vaccines or therapies that activate the inflammatory signaling pathways that target the tumor and specifically block inhibitory pathways in the immunosuppressive tumor microenvironment although challenging may be the way forward (Figure 2).

There have already been a number of studies in mice that have demonstrated the benefits of using combination approaches that

![Diagram of immune system and tumor microenvironment]

Figure 2. Combination immunotherapeutic/vaccine approaches against tumors. (a) In the initial stages of immune response against tumors, the local tissue resident innate immune cells, including macrophages and DCs recognizes the tumor antigens, are activated and migrate to regional lymph nodes via the lymphatic vessels where they activate the naive T cells by presenting the tumor antigens. Co-stimulatory and co-inhibitory molecules on APC interact with ligands on T cells, leading to the proliferation of effector and regulatory T cells respectively. A high percentage of immunosuppressive cells, including Treg cells, MDSCs, M2 macrophages, infiltrate the tumor microenvironment, which inhibit the effector immune responses against tumor. (b) Combination vaccine or immunotherapeutic approaches that target the immune response pathways are effective means of enhancing antitumor immunity. Strategies that combine innate cell activation with TLR agonists with depletion or inhibition of Tregs and MDSCs, or blockade of co-inhibitory molecules can enhance effector T cell responses against the tumor.
target multiple points in the immune system to enhance the antitumor immunity. For example, a study has demonstrated that the efficacy of DC vaccine against B16 melanoma in mice can be enhanced by the gene silencing of TGF-β1, which reduces the tumor-associated Treg cells.

Furthermore, it has been shown that a single dose of cyclophosphamide can reduce the numbers of tumor cells and enhance the efficacy of the vaccine. This suggests that the combination of tumor-specific immunotherapy and chemotherapeutics is a promising strategy to enhance antitumor immunity.

We have also studied the effects of tumor-specific immunotherapy on the renal cell cancer vaccine (MAA901), leading to prolonged survival of cancer patients after vaccination. This combination therapy is expected to improve the survival rates of patients with solid tumors.

Conflict of Interest

KHC, MK, IA, and MB are employees of OncoGenex Inc. MM declares no conflict of interest.

Acknowledgements

This research was supported by grants from Science Foundation Ireland.

References


