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Review Article

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Immunotherapy: Challenges

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Abstract

The knowledge that the body possesses natural defenses to combat cancer existed long before the modern period, with multiple anecdotal reports of tumors miraculously disappearing, sometimes spontaneously or after a febrile or infectious episode. Spontaneous tumor regression of untreated malignant tumors is currently a well-accepted albeit rare phenomenon, and it is recognized that immunosuppression is associated with a higher cancer risk. The treatment of bladder carcinoma by intravesical administration of live attenuated Bacillus Calmette-Guérin bacteria was shown to be very effective in 1976 and is now standard treatment. Cancer immunotherapy is a promising way to eliminate tumor cells by using the patient's own immune system. Selecting the appropriate animal models to develop or validate preclinical immunotherapeutic trials is now an important aspect of many cancer research programs. Here we discuss the advantages and limitations of using genetically engineered immunodeficient mouse models, patient-derived xenografts (PDXs), and humanized mouse models for developing and testing immunotherapeutic strategies.

Introduction

Immunotherapy

A type of therapy that uses substances to stimulate or suppress the immune system to help the body fight cancer, infection, and other diseases. Some types of immunotherapy only target certain cells of the immune system. Others affect the immune system in a general way. Types of immunotherapy include cytokines, vaccines, bacillus Calmette-Guerin (BCG), and some monoclonal antibodies. Immunotherapy uses the body's immune system to fight cancer. This animation explains three types of immunotherapy used to treat cancer: nonspecific immune stimulation, T-cell transfer therapy, and immune checkpoint inhibitors.

Cancer immunotherapy is the artificial stimulation of the immune system to treat cancer, improving on the immune system's natural ability to fight cancer. It is an application of the fundamental research of cancer immunology and a growing subspeciality of oncology.

Adoptive cell therapy

Adoptive cell transfer is the transfer of cells into a patient. The cells may have originated from the patient or from another individual. The cells are most commonly derived from the immune system with the goal of improving immune functionality and characteristics.

Adoptive cell therapy that uses **T cells** from a donor is being studied in the treatment of some types of cancer and some infections. Also called **adoptive cell** transfer, **cellular adoptive** immunotherapy, and **T-cell** transfer **therapy**

Cancer vaccines

ancer vaccine is a vaccine, that either treats existing cancer or prevents development of a cancer. Vaccines that treat existing cancer are known as *therapeutic* cancer vaccines.

Some/many of the vaccines are "autologous", being prepared from samples taken from the patient, and are specific to that patient.

Some researchers claim that cancerous cells routinely arise and are destroyed by the immune system;and that tumors form when the immune system fails to destroy them Oncophage was approved in Russia in 2008 for kidney cancer. It is marketed by Antigenics Inc. Sipuleucel-T, Provenge, was approved by the FDA in April 2010 for metastatic hormone-refractory prostate cancer. It is marketed by Dendreon Corp. Canvaxin, Genitope Corp (MyVax personalized immunotherapy), and FavId (Favrille Inc) are examples of cancer vaccine projects that have been terminated, due to poor phase III results. Cancer vaccines seek to target a tumor-specific antigen as distinct from self-proteins. Selection of the appropriate adjuvant to activate antigen-presenting cells to stimulate immune responses, is required. Bacillus Calmette-Guérin, an aluminum-based salt, and a squalene-oil-water emulsion are approved for clinical use. An effective vaccine also should seek to stimulate long term immune memory to prevent tumor recurrence. Some scientists claim both the innate and adaptive immune systems must be activated to achieve total tumor elimination

Recommendations

In January 2009, a review article made recommendations for success as follows

Target settings with a low disease burden.

Conduct randomized Phase II trials so that the Phase III program is sufficiently powered.

Do not randomize antigen plus adjuvant versus adjuvant alone. The goal is to establish clinical benefit of the immunotherapy (i.e., adjuvanted vaccine) over the standard of care. The adjuvant may have a low-level clinical effect that skews the trial, increasing the chances of a false negative.

Base development decisions on clinical data rather than immune responses. Time-to-event end points are more valuable and clinically relevant.

Design regulatory into the program from inception; invest in manufacturing and product assays early.

Immune checkpoints

Immune checkpoints are regulators of the **immune** system. These pathways are crucial for self-tolerance, which prevents the **immune** system from attacking cells indiscriminately. Inhibitory **checkpoint** molecules are targets for cancer immunotherapy due to their potential for use in multiple types of cancers.

Immune checkpoints are regulators of immune activation. They play a key role in maintaining immune homeostasis and preventing autoimmunity. In cancer, immune checkpoint mechanisms are often activated to suppress the nascent anti-tumor immune response. This has led to the development of several checkpoint inhibitor antibody drugs that are currently being tested in clinical trials or have been approved for a number of cancers. This mini-review provides an overview of the mechanisms of action of major immune checkpoint molecules as well as highlights checkpoint inhibitor antibodies in clinical development.

T cell immunoglobulin mucin 3 (TIM-3)

TIM-3 was discovered in 2002 as a marker for interferon-gamma (IFN-γ) producing $CD8^+$ T cells (Kim et al. 2015). It is a glycoprotein that has extracellular immunoglobulin and mucin domains. TIM-3 is expressed on a number of cells such as activated T cells as well as tissues such as the liver, small intestine, thymus, kidney, spleen, lung, muscle and brain (Wada and Kanwar 1997). The most prominent ligand for TIM-3 is galectin. However, other ligands have been identified such as phosphatidyl serine and high mobility group box 1 (HMGB1) (Zhu et al. 2005, Gorman and Colgan 2014).

Signaling through TIM-3 is dependent on phosphorylation at Y265 by inducible T cell kinase (van de Weyer et al. 2006). Studies in autoimmune models also show that the cytoplasmic protein Bat3 functions as an adapter protein to modulate cell proliferation. In this context, Bat3 binds TIM-3 at rest and protects the T cell from TIM-3 signaling. However, when TIM-3 binds to galectin 9, Bat3 dissociates from TIM-3, which leads to decreased production of IFN-γ and reduced T cell proliferation (Rangachari et al. 2012).

Killer immunoglobulin-like receptors (KIRs)

KIRs are a broad category of receptors that primarily bind MHC I molecules and inhibit NK cell function (Lanier 2008). In addition to NK cells, these receptors are also expressed on T cells (specifically tumor-associated cytotoxic T cells) and APCs (Mingari et al. 2005). However, their inhibitory role on T cells and APCs is less well studied (Pardoll 2012).

KIRs generally contain 2-3 immunoglobulin (Ig) ectodomains and cytoplasmic tails of various lengths (Long et al. 1997). However, they can be separated into two distinct subclasses based on structure and function. Some KIRs are activating and have truncated cytoplasmic tails and a positively charged residue in their transmembrane domain. In contrast, others are type II transmembrane receptors containing two immune receptor tyrosine-based inhibitory motifs (ITIMs), which facilitate inhibitory signaling. ITIMs mediate downstream signaling leading to negative regulation of NK cell function, reduction of NK cell mediated lysis and NK tolerance to self (Kim et al. 2015).

KIRs induce NK cell tolerance through a process called licensing. During this process, the KIR recognizes a self MHC I molecule and prevents NK cell activation against self-tissue and auto-antigens (Yu et al. 2009). There are more than 20 KIRs, with many demonstrating specificity for subsets of human leukocyte antigens (HLAs) and allele specificity.

The 4-1BB receptor (also known as CD137) belongs to the tumor necrosis factor receptor (TNFR) superfamily. It is expressed on stimulated $CD4^+$ and $CD8^+$ T cells, activated NK cells, neutrophils and dendritic cells (Kim et al. 2015). It is a type II transmembrane glycoprotein that binds the 4-1BB ligand expressed on activated macrophages and B cells (Kim et al. 2015). In contrast to the other immune checkpoint molecules previously discussed, 4-1BB is an activating checkpoint. Upon ligation of the 4-1BB receptor, NF-κB, c-Jun and p38 signaling pathways become activated (Cannons et al. 2000). This ultimately promotes survival and pro-inflammatory pathways. In $CD8^+$T cells, 4-1BB receptor activation induces survival by upregulating the expression of anti-apoptotic genes BcL-xL and Bfl-1 (Lee et al. 2002). The main role of 4-1BB therefore is to boost the immune response.

Glucocorticoid-induced TNFR family related gene (GITR)

Similar to the 4-1BB receptor, GITR also belongs to the TNFR superfamily. It was initially identified as a marker of Tregs; however it is now known to also be constitutively expressed on effector $CD4^+$ and $CD8^+$ T cells (McHugh et al. 2002). The human ligand for GITR (GITRL) is constitutively expressed on APCs in secondary lymphoid organs and on non-lymphoid tissues (Kim et al. 2015). Once GITR engages with its ligand GITRL, the downstream signaling ultimately results in attenuation of Treg responses and enhancement of effector T cell responses (Kim et al. 2015). Therefore, like 4-1BB, GITR is also an activation immune checkpoint that enhances host immune responses. However, studies show that overexpression of GITR or experimental agonism of the receptor is associated with autoimmunity and inflammatory indications such as asthma and post-stroke states (Kohm et al. 2004, Patel et al. 2005, Takata et al. 2012).

Blockade of immune checkpoints for cancer therapy

Cancer growth is partly mediated by immune suppression induced by cancers. Studies have demonstrated that tumors can activate suppressive immune checkpoint pathways in order to diminish the immune response to the tumor (Finn 2012). Scientists therefore investigated whether blockade of key immune checkpoint pathways could induce effective anti-tumor immunity. Initial preclinical research indicated that antibody blockade of the immune checkpoint molecule CTLA-4 resulted in successful anti-tumor immune responses in murine cancer models (Leach et al. 1996, van Elsas et al. 1999). Based on these findings, CTLA-4 was the first immune checkpoint molecule to be clinically targeted. This was then followed by antibodies

targeting the PD-1/PD-L1 pathway. To date, the most advanced agents in clinical trials are those targeting CTLA-4 and PD-1/PD-L1 (Figure 1). Below we discuss the current inhibitor antibodies in clinical development.

Inhibitor antibodies targeting the CTLA-4 immune checkpoint

Ipilimumab was the first anti-CTLA-4 drug developed. It is a fully humanized Ig G1 kappa monoclonal antibody that antagonizes CTLA-4 and inhibits ligand binding (Morse 2005). Two phase III studies involving patients with advanced melanoma showed that ipilimumab improved overall survival by several months. This led to its approval for the treatment of melanoma by the United States Food and Drug Administration (FDA) and the European Medicines Agency (Hodi et al. 2010, Robert et al. 2011). Pooled analysis of data from ipilimumab trials demonstrates that approximately 20% of patients will have long term survival of at least 3 years after ipilimumab therapy (Postow et al. 2015). Ipilimumab is still currently being evaluated for application in other indications, with significant attention to effective combination strategies with other checkpoint inhibitor antibodies.

The second anti-CTLA-4 antibody currently being evaluated in clinical trials is tremelimumab, a fully human IgG2 monoclonal antibody. It is being investigated as a monotherapy or in combination with durvalumab (a PD-L1 targeted antibody) in non-small cell lung (NSCLC), head and neck, gastric, pancreatic, blood cancers and hepatocellular carcinoma. It has also been tested as a potential treatment for malignant mesothelioma and advanced melanoma.

A phase III clinical trial comparing tremelimumab treatment to standard-of-care chemotherapy (dacarbazine/temozolomide) in patients with advanced melanoma demonstrated disappointing results. Although some patients experienced a durable response, tremelimumab did not demonstrate significant survival advantage over standard-of-care chemotherapy treatment (Ribas et al. 2013). Recently, a phase IIb trial assessing the efficacy of tremelimumab as a monotherapy in mesothelioma also reported dismal results, as the trial failed to meet its primary endpoint of improving overall survival (AstraZeneca 2016).

Another phase Ib study investigating the anti-tumor activity of tremelimumab and durvalumab in locally advanced or metastatic NSCLC patients demonstrated significant antitumor activity. Notably, the anti-tumor effect of the combination therapy was independent of PD-L1 status, and phase III studies are now on-going (Antonia et al. 2016). Further research is also being conducted to identify biomarkers for predicting which patients are likely to respond to anti-CTLA-4 therapies.

Inhibitor antibodies targeting the PD-1/PD-L1 immune checkpoint

Owing to the success of ipilimumab, several anti-PD-1 and anti-PD-L1 antibodies have been developed. Those that target PD-1 include nivolumab, pembrolizumab, and pidilizumab. PD-L1 targeted antibodies are atezolizumab (MPDL3280A), durvalumab (MEDI4736), BMS-936559 and MSB0010718C. In addition, a PD-L2 fusion protein that depletes PD-1 positive T cells is also under clinical development (Infante et al. 2013).

The results observed in clinical studies targeting the PD-1/PD-L1 pathway have been encouraging since higher response rates were reported than in CTLA-4 blockade studies (Sharon et al. 2014). Furthermore, PD-1/PD-L1 blockade generally results in less severe adverse effects, although fatal pneumonitis was observed in 1% of patients in an anti-PD-1 antibody clinical trial (Topalian et al. 2012).

A phase III study comparing nivolumab treatment to standard chemotherapy (dacarbazine or carboplatin/paclitaxel) involving melanoma patients who did not respond to ipilimumab treatment demonstrated a 32% overall response rate with nivolumab compared to only 11% with chemotherapy alone (Weber et al. 2015).

Pembrolizumab also demonstrated significant efficacy in clinical trials, leading to its approval by the FDA for treating patients with melanoma who were previously treated with ipilimumab and, if relevant, a BRAF inhibitor (Robert et al. 2014). Pidilizumab on the other hand is primarily being evaluated in hematological cancers and has demonstrated favorable responses as a monotherapy and in combination with other therapies such as

rituximab (Berger et al. 2008, Armand et al. 2013, Westin et al. 2014).

Targeting PD-L1 has also demonstrated impressive results in the clinic. Phase II and III studies involving atezolizumab demonstrated consistent results in patients with NSCLC (Fehrenbacher et al. 2016, Rittmeyer A et al. 2017). Compared to docetaxel chemotherapy, treatment with atezolizumab resulted in a 4.2 month and 2.9 month improvement in overall survival in the phase II and III trials, respectively. This led to the FDA approval of atezolizumab in October 2016 for the treatment of patients with metastatic NSCLC whose disease progressed during or following platinum-containing chemotherapy.

Durvalumab is currently being tested in clinical trials as a monotherapy for metastatic urothelial cancer, and has demonstrated a manageable safety profile and significant clinical activity (Massard et al. 2016).

As the inhibitor antibodies discussed above move through clinical development and to patients, there is likely to be further opportunities to improve their effect. Particularly, more research is now being conducted to evaluate combination therapies focusing on the complementary mechanisms of action of these antibody drugs.

Conclusion

The immune system has evolved to protect us from infection. The human immune system is immensely complex and the drawback of developing an immune system that may recognize and respond to all infections is the potential for hypersensitivity reactions. These manifest as allergic responses to environmental agents and autoimmune responses to self-antigens. Equally, the immune system has developed sophisticated regulatory mechanisms to protect against rejection of the human allograft during pregnancy and reduce the risk of autoimmune diseases. These immune regulatory mechanisms serve as barriers to effective cancer immunity: the challenge to cancer control and eradication is how to have one without the other, i.e., how to promote effective cancer immunity without the toxic side effects of autoimmune diseases. Recent breakthroughs in the use of checkpoint inhibition, when combined with cancer vaccination, will make this feasible: the key factor is to target the relevant cancer antigen. For autoimmune diseases, we have depended on non-specific immunosuppressive drugs for far too long. We have failed to learn from the allergy field where effective immunotherapy is achieved by targeted desensitization using allergy associated antigens. The antigen-specific immunotherapies referred to in this perspective article herald a new era of immunotherapy for autoimmune diseases where again the key factor is to target the relevant antigen, in this case the self-antigen.

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