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Immunotherapeutic approaches for cancer therapy: An updated review

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Abstract

In spite of specific immune effector mechanisms raised against tumor cells, there are mechanisms employed by the tumor cells to keep them away from immune recognition and elimination; some of these mechanisms have been identified, while others are still poorly understood. Manipulation or augmentation of specific antitumor immune responses are now the preferred approaches for treatment of malignancies, and traditional therapeutic approaches are being replaced by the use of agents which potentiate immune effector mechanisms, broadly called "immunotherapy". Cancer immunotherapy is generally classified into two main classes including active and passive methods. Interventions to augment the immune system of the patient, for example, vaccination or adjuvant therapy, actively promote antitumor effector mechanisms to improve cancer elimination. On the other hand, administration of specific monoclonal antibodies (mAbs) against different tumor antigens and adoptive transfer of genetically-modified specific T cells are currently the most rapidly developing approaches for cancer targeted therapy. In this review, we will discuss the different modalities for active and passive immunotherapy for cancer.

Keywords: cancer, cancer stem cell, dendritic cell, immunotherapy, monoclonal antibody, vaccination

Historical background

In 1909, the Nobel Prize winner Paul Ehrlich first proposed the concept that transformed cells continuously arise in our bodies, and elements of the immune system contribute to the control of these transformed cells and eradicate these malignant cells before they are manifested clinically (Kim et al. 2007, Ehrlich and Himmelweit 1956).

In the mid-20th century, Burnet and Thomas developed the immune surveillance hypothesis which postulated that the immune system very efficiently destroys malignant cells, and experimental results showing strong immune-mediated rejection of transplanted tumors in mice supported this idea. However, this hypothesis was challenged by experimental data and clinical observations in the 1970s, which indicated that immunosuppressive medication for organ transplantation did not increase the incidence of solid tumors in areas such as colon, lung and breast (Burnet 1957, Newstead 1998).

Although the immune system does not play the central role in the immune surveillance as suggested by Burnet and Thomas, more recent clinical studies provide evidence that immune effector cells and mediators such as B, T, natural killer (NK), natural killer T (NKT) cells, and cytokines contribute to the control of premalignant cells (Riether et al. 2013).

Despite these effector mechanisms, malignant cells are able to evade immune responses. In this regard, immunotherapy for the treatment of cancer has been used for decades and has been dramatically developed during recent years. In this review, we provide a general overview of cancer-active immunotherapy [for example, tumor vaccination using tumor-derived peptide and protein, DNA and dendritic cell-based vaccine, and adjuvant therapy using BCG (Bacillus Calmette-Guérin), and cytokines] and passive immunotherapy [for example, using monoclonal antibodies (mAbs) and adoptive T cell therapy], as well as approaches involving the targeting of cancer stem cells (CSCs) to overcome cancer relapse and provide resistance.

Tumor escape from immune system

In spite of several mechanisms active in the immune system to recognize and eliminate tumor cells, known as the "elimination phase", some variants of these cells selectively acquire increased resistance against immune responses (equilibrium phase). Thereafter, resistant cells continue to grow by employing mechanisms to evade the immune responses (escape phase). During this phase, tumor cells develop resistance against both innate and adaptive immune mechanisms and the clinical manifestations of tumor develop. All the three above-mentioned phases are collectively called "cancer immunoediting", believed to be a phenomenon

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derived by immune responses (Dunn et al. 2002, Finn 2012). In the escape phase, resistant tumor cells develop two classes of mechanisms to avoid being killed by what is known as "immunosurveillance": (I) immunologic ignorance and tolerance, and (II) negative regulation of immune cells (Bhutia et al. 2010). The selection of tumor cells with weak or no expression of specific antigens, defects in the expression of MHC molecules and antigen-processing and presentation, and the presentation of tumor antigen-derived peptides with weak or no expression of costimulatory and adhesion molecules are mechanisms proposed to be developed by tumor cells than enable them to be tolerated or ignored (Costello et al. 1999, Maeurer et al. 1996, Igney and Krammer 2002, Flynn and Stockinger 2003). These mechanisms are not recently discovered, but the induction of regulatory mechanisms continues to be clarified. So far, expression of FasL to induce apoptosis in immune effector cells (a phenomenon called Fas counterattack) (Strand and Galle 1998), expression of programmed death-ligand 1 (PD-L1) to inhibit immune effector mechanisms (Iwai et al. 2002), production of immunosuppressive cytokines, for example, transforming growth factor (TGF)-β (Pasche 2001), interleukin (IL)-10 (Salazar-Onfray 1999, Mocellin et al. 2005), vascular endothelial growth factor (VEGF) (Gabrilovich et al. 1996), induction of T cell anergy via production of indoleamine 2,3-dioxygenase (IDO) and depletion of tryptophan (Mellor et al. 2003), and the release of exosomes or microvesicles by tumor cells, have been revealed (Whiteside 2005, Taylor et al. 1988, Kim et al. 2005).

Adjuvant therapy

The effect of an adjuvant in immunotherapy is in potentiating immune response against tumor cells. As discussed earlier, different approaches have been used to vaccinate cancer patients and raise specific immune responses for treatment. Parallel administration of an adjuvant could induce more potent and effective immune responses and therefore increase the efficacy of active immunotherapy. As cancer patients are generally immunocompromised and vaccination is usually done by self-derived antigens, adjuvants for therapy should be more potent than adjuvants for prophylaxis, but with acceptable toxicity and safety. Some agents have been used for this purpose (Mesa and Fernandez 2004).

Nowadays, monotherapy by cytokines and other immunological response-modifiers have been considered as immunotherapy by adjuvants or in "adjuvant therapy" for cancer. The best-defined example is the intravesical administration of BCG for treatment of bladder cancer. The exact mechanism of such treatment is not fully understood, but it has been proposed that the presence of bacteria in malignant tissue could induce inflammation and the recruitment of immune cells that eventually lead to the elimination of cancerous cells (Meyer et al. 2002). Interferon (IFN)-α is currently used as the treatment regimen for melanoma (Hauschild 2009), AIDS-related Kaposi's sarcoma (Abrams and Volberding 1986), renal cancer (Minasian et al. 1993), hairy cell leukemia (HCL) (Ahmed and Rai 2003), and chronic myelogenous leukemia (CML) (Bonifazi et al. 2001). The overall mechanism of IFN-α is proposed to be increased expression of MHC I and antigen presentation for better and more effective antitumor immune responses (Kirkwood 2002). IL-2 has been used to reverse dysfunction of immune effector cells in the treatment of metastatic melanoma (Atkins et al. 1999) and renal cell carcinoma (Dutcher 2011). Recently, stimulating innate immunity by the ligands of toll-like receptors (TLRs) or their analogs has been considered as a new category of cancer immunotherapeutics. Imiquimod activates TLR7 on immune cells, and is used as cream for treatment of basal cell carcinoma (BCC), the most common form of skin cancer (Oldfield et al. 2005). Resiquimod (R-848), on the other hand, stimulates TLR7 and TLR8 and is used to cure viral skin lesions and skin cancers (Meyer et al. 2013).

Passive immunotherapy

Therapeutic monoclonal antibodies

More than 100 years ago, using "magic bullets" to kill tumor cells and treat cancers was proposed by Paul Erlich. This interesting idea was initially promising, but encountered some clinical and experimental obstacles, including unknown purity of antibody preparations and therefore induction of some unwanted reactions, and failure to recognize definite tumor targets (Oldham 1983, Scott et al. 2012). Several years later, the advent of mAb production technology developed by the tireless efforts and experiments of George Köhler and Cesar Milstein in 1975 (Kohler and Milstein 1975), solved the problems. Subsequently, a vast number of mAbs was produced against different known targets for diverse clinical and diagnostic proposes. The first Food and Drug Administration (FDA)-approved therapeutic mAb was anti-CD3 mouse mAb, so-called OKT3, to prevent rejection of kidney allograft (Group 1985). The murine origin of OKT3, production of human anti-mouse antibody (HAMA) in humans, and also improper interaction of mouse mAb with human effector molecules, that is, C1 and FcγRs, greatly limited the applications of mouse mAbs in chronic clinical administrations (Baker et al. 2010). As shown in Table I, only two other FDA-approved mouse mAbs cancer therapeutics are designed for clinical settings, as conjugated platforms to deliver the radioisotope payload to the tumor mass. By exchanging the constant (c) regions of mouse mAb for human ones (Figure 1), "chimeric" mAb was introduced with better biologic effects and lower immunogenicity in humans (Neuberger et al. 1985). FDA-approved chimeric mAbs for cancer therapy have been listed in Table I. As antibody specificity is determined by the complementarity-determining regions (CDRs) of variable (V) domains of mAb, but not the whole V domain, CDRs from mouse mAb were "grafted" onto the backbone of the human Ig molecule to produce the third generation of therapeutic mAbs, called "humanized" mAbs (Jones et al. 1986) (Figure 1). FDA-approved humanized mAbs for cancer therapy have also been listed in Table I. However, because the process of producing humanized mAb with better efficacy consumed too much time and effort, and the immunogenicity of the end product was too low, a fourth generation of therapeutic mAbs were produced using

Table I. FDA-approved monoclonal antibodies for cancer therapy.

Name of Antibody	Brand name	Year of Approval	Target	Indication (disease)
Mouse mAb				
Ibritumomab-^{90}Y	Zevalin	2002	CD20	NHL
Tositumomab-^{131}I	Bexxar	2003	CD20	NHL
Chimeric mAb				
Rituximab	Rituxan, Mabthera	1997	CD20	NHL
Cetuximab	Erbitux	2004	EGFR	Colorectal cancer, Head and neck cancer
Brentuximab vedotin	Adcetris	2011	CD30	ALCL and HL
Humanized mAb				
Trastuzumab	Herceptin	1998	ErbB2	Breast cancer
Gemtuzumab	Mylotarg	2000	CD33	AML
Alemtuzumab	Campath	2001	CD52	CLL
Bevacizumab	Avastin	2004	VEGF	Colorectal cancer
Fully-human mAb				
Panitumumab	Vectibix	2006	EGFR	Colorectal cancer
Ofatumumab	Arzerra	2009	CD20	CLL
Ipilimumab	Yervoy	2011	CTLA-4	Melanoma
Denosumab	XGEVA	2011	RNAKL	Breast and prostate carcinoma

NHL, Non-Hodgkin lymphoma; ALCL, Anaplastic large cell lymphoma; HL, Hodgkin lymphoma; AML, Acute myelogenous leukemia; CLL, Chronic lymphocytic leukemia.

advanced in vitro and in vivo methods such as phage display (Smith 1985), the Epstein–Barr virus (EBV)-transformation of B cells (Borrebaeck 1989), and the use of transgenic mice (Lonberg 2008). Fourth generation mAbs are "fully-human" with any part of mouse origin. It is believed that these antibodies are not immunogenic, but allotypic differences between therapeutic mAb and recipient patient, and also idiotypic determinants residing in the antigen-binding site of therapeutic mAb can induce production of anti-antibodies and lead to neutralization of the drug and some clinically adverse effects (Harding et al. 2010).

The mechanisms of action of therapeutic mAbs to induce anti-tumor effects have been explored exclusively with respect to antibody-dependent cell-mediated cytotoxicity (ADCC) for Herceptin (Lewis et al. 1993), Rituximab (Reff et al. 1994), and Ofatumumab (Teeling et al. 2004); complement-dependent cytotoxicity (CDC) for Rituximab (Reff et al. 1994), Alemtuzumab (Zent et al. 2008), and Ofatumumab (Teeling et al. 2004); interaction with growth factor receptors and inhibition of survival signaling for Herceptin (Lewis et al. 1993), Cetuximab (Huang et al. 1999) and Panitumumab (Yang et al. 1999); antiangiogenic effect for Bevacizumab (Kim et al. 1992); prevention of bone destruction due to breast and prostate cancers for Denosumab (Pageau 2009, Smith et al. 2012); and delivery of cytotoxic agents, for example, calicheamicin, yttrium-90, iodine-131, and monomethyl auristatin E to tumor cells for Gemtuzumab (Breccia and Lo-Coco 2011) Ibritumomab (Jacobs 2007), Tositumomab (Rutar et al. 2001) and Brentuximab (Vaklavas and Forero-Torres 2012), respectively. It is noteworthy that each therapeutic mAb could also have its own specific function according to the nature of the targeted antigen. For example, Herceptin recognizes and binds to HER2 molecules and leads to internalization and inhibition of auto-cleavage of HER2. On the other hand, dimerization of HER2 to other members of the HER family could be inhibited by Herceptin (Vu and Claret 2012). Additionally, therapeutic mAb against CTLA-4 (Ipilimumab) antagonizes CD80 and CD86 molecules on antigen-presenting cells (APCs), and as a result, hinders inactivation of tumor-specific effector T cells (Tarhini et al. 2010).

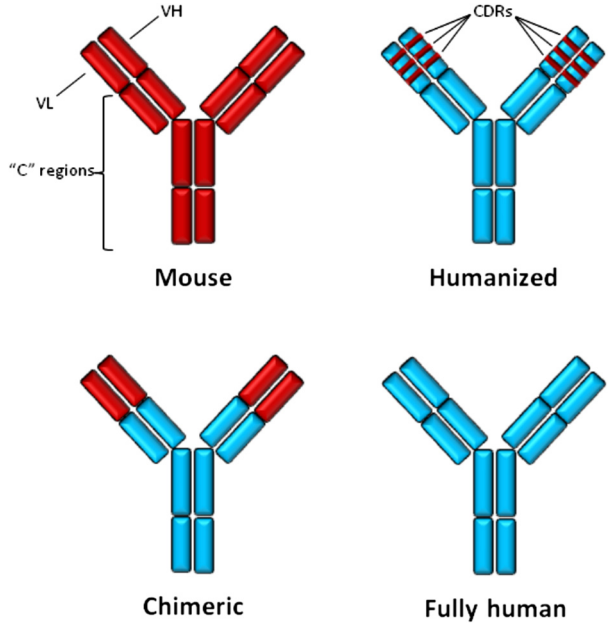

Figure 1. Generation of therapeutic monoclonal antibodies.

New approaches for interfering with inhibitory pathways of the immune system to obtain prolonged antitumor cellular responses have been developed. Blocking or antagonistic mAbs against T cell immunoglobulin and mucin domain-containing protein 3 (TIM-3), lymphocyte activating gene 3 (LAG-3), B and T lymphocyte attenuator (BTLA), and programmed death-1 (PD-1) and its ligand PD-L1 have led to promising antitumor effects (Pardoll 2012, Kyi and Postow 2013). On the other hand, some experiments have been carried out to potentiate antitumor responses by administering agonistic mAbs against costimulatory and activatory molecules on T lymphocytes, for example, CD137, OX-40, 4-1BB (CD137), GITR, and CD27 (Mittler et al. 2004, Moran et al.

2013, Schaer et al. 2012, Vinay and Kwon 2012, Riether et al. 2012).

Adoptive T cell therapy

Adoptive transfer of ex vivo-enriched and expanded tumor-specific T lymphocytes has long been proposed and performed for treatment of cancers refractory to conventional therapeutic approaches (Yee 2013). The common modalities for adoptive transfer of autologous or allogeneic T cells encounter some problems, including the time consuming processes for development of desired cell populations, short in vivo half-life, and self-MHC restriction of T cells for activation (Riether et al. 2013). Advances in genetic engineering of T cells has given rise to introduce of chimeric antigen receptor (CAR) T cells or "T-body" technology (Dotti et al. 2009). A CAR consists of an extracellular recognition domain, including variable domains of heavy (VH) and light (VL) chains derived from tumor antigen-specific B cells. The recognition unit extends to a spacer and then the transmembrane domain and intracellular signaling motifs derived from stimulatory molecules, for example, CD28, CD3 ζ, 4-1BB, and OX40 (Cartellieri et al. 2010, Han et al. 2013). According to cytoplasmic signaling domains built into a CAR, there are three generations of CARs containing intracellular motifs of one, two, or three of the above-mentioned molecules (Figure 2). Genes coding for VH and VL domains and also signaling motifs (collectively, scFV) are cloned into a retroviral vector and transfected in T lymphocytes derived from the patient's body. Because of the nature of retroviral vectors, inserted genes are integrated into the genome of T cells and these cells bear their own "artificial" specificity throughout their lifecycle. After re-transfusion of engineered T cells, they recognize tumor-specific antigens (TSAs) and respond with activation, proliferation, and exertion of effector functions to kill tumor cells. Antigen recognition by CARs brings along some advantages including non-MHC restricted recognition and T cell proliferation, the recognition of not only protein but other types of antigens, capability of giving desired specificity to both $CD4^+$ and $CD8^+$ T cells, and lower probability of eliciting unwanted responses especially autoimmunity (Sadelain et al. 2013).

Several antigenic targets of hematologic and solid tumors have been selected, and CAR T cells have been designed and used in murine models and also in clinical trials (Kershaw et al. 2013). The most frequent target for CAR T cell therapy has been CD19 in several CD19-expressing malignancies. CTL019, formerly called CART19, is one of the most promising CAR T cell therapies designed for treatment of ALL. CT019 resulted in complete remission in a study of two children with relapsed chemotherapy- refractory ALL (Davila et al. 2013). There are also ongoing studies on application of CTL019 therapy in B-CLL.

Cancer vaccines

History

Vaccination is a very old medical procedure that induces the immune system's functions and brings a long-lasting immunologic memory to protect the body against foreign elements such as microbes (Lambert et al. 2005). Curiosity in vaccination against malignancy commenced around the 1900s, when the effectiveness of microbial vaccines had been already proved. The thought was rational: to apply killed or inactive malignant cells using a similar approach, but in the context of a tumor. Recently, advances in active immunotherapy for prevention and treatment of cancers has been emphasized (Jager et al. 2002). By priming or boosting the immune system's natural capability, cancer vaccines are effective medicines that are categorized in a class of therapeutics known as biologic response modifiers (BRM). Cancer vaccines achieve this effect by introducing single or combined molecules known as tumor antigens into the immune system. Dendritic cells, the most proficient APCs, can take-up tumor antigens, and depending on the environmental and inflammatory conditions, present the antigens at the tumor sites or at lymphoid organs to prime, sustain, or abrogate the

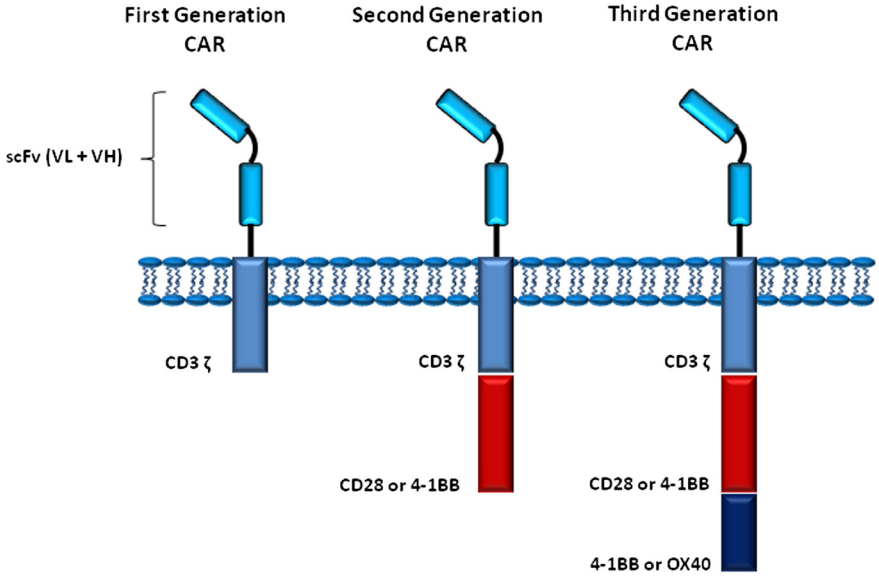

Figure 2. Different generations of CARs used in therapeutic approaches.

tumor-specific immune response. Due to the self-origin of tumor cells and the natural immuno-evasive and suppressive mechanisms of tumor cells, a few cancer vaccines have been approved for clinical use (Tabi and Man 2006).

There are two classes of tumor antigens, including abnormal self-antigens (ASAs) and TSAs (Neville et al. 1975). ASAs are usually embryonal and developmental antigens not normally expressed in adult tissues, normal proteins with unusual glycosylation patterns, or overexpressed self-antigens. TSAs spawn following somatic mutations or damages in the germline DNA that lead to errors in the mature mRNA or to fusion proteins (Finn 2006). Not all such mutations change the immunogenicity of tumor cells, and the question of the degree to which TSAs comply with the requirements for fitting to the MHC antigen-binding site (Segal et al. 2008) remains unanswered. Recently, enormous TSAs have been discovered which may be fitting for antigen-defined cancer vaccines and include antigens discovered as deriving from somatic mutations in oncogenes or tumor suppressor genes (for example, RAS, BCR/ABL, BRCA1,2, HER2,3 and P53), cancer/testis antigen (NY-ESO-1), developmental antigens (for example, MAGE, tyrosinase, gp100), and overexpressed antigens (for example, oncofetal antigens, carcinoembryonic antigen, α-fetoprotein) (Greiner et al. 2002, De Giovanni et al. 2004, Sobol 2006, Theobald et al. 1995).

Great numbers of potential tumor antigens have been described by the Academy of Cancer Immunology (http://www.cancerimmunity.org/peptidedatabase/Tcellepitopes.htm). Moreover, the Cancer Genome Atlas (TCGA) has recently revealed large numbers of potential tumor antigens in different types of solid tumors.

Despite defined tumor antigen-based vaccines (for example, DNA and peptide-based vaccines), some more recent and unconventional vaccine platforms (for example, tumor-cell-based vaccines, allogeneic tumor heat-shock proteins) depend on the construction of shared antigens between similar tumor cells and therefore do not require identification of certain tumor antigens in advance (Schreiber et al. 2010).

Cancer-preventive and treatment vaccines

There are two basic classes of cancer vaccines. Preventive vaccines, which are supposed to prevent initiation of malignant transformation in normal cells of healthy subjects, and treatment vaccines, which are intended to treat an established cancer by intensification of the immune system's antitumor capability (Lollini et al. 2006). Three cancer-preventive vaccines have been released in the United States, and one cancer treatment vaccine also has recently become available. Cancer-preventive vaccines target infectious agents that cause or are associated with the development of cancer (Doorbar 2006, Frazer et al. 2007). The FDA has just approved Gardasil, manufactured by Merck & Company, and Cervarix, manufactured by GlaxoSmithKline, that protect against infection by HPV—types 16 and 18—that cause approximately 70 percent of all cases of cervical cancer (Doorbar 2006). The FDA has also approved a cancer-preventive vaccine that immunizes against the HBV infection which can lead to hepatocellular carcinoma. The original HBV vaccine was approved in early 1980s, making it the first-in-class cancer preventive vaccine to be successfully developed. Today, most newborns in the United States are vaccinated against HBV (Yaddanapudi et al. 2013).

Cancer treatment vaccines are supposed to treat tumors that have already established and are well-grown. They have been proven more difficult and challenging to produce than cancer preventive vaccines (Rosenberg et al. 2004). Cancer treatment vaccines must meet more demands. Actually, they must stimulate immune responses that are specific and strong enough against the proper target antigen and cells, to defeat the barriers of immuno-evasion and suppression that cancer cells exploit to protect themselves from immune responses. Using whole tumor cell extract, tumor antigens, whole tumor cells, as well as costimulatory molecules and TSA-encoding recombinant DNA, cancer treatment vaccines are poised to delay or hold back transformed cell growth and to block tumor recurrence. Scientists are developing methods of immunotherapy that can be used to prime/boost tumor-specific immune responses that are currently being evaluated as treatment vaccines (Antonia et al. 2004, Yaddanapudi et al. 2013).

In 2010, the FDA approved the first-in-class cancer treatment vaccine, sipuleucel-T (Provenge®, manufactured by Dendreon), for treatment of hormone-refractory prostate cancer and metastatic prostate cancer (Antonia et al. 2004). It is designed to trigger an immune response to prostatic acid phosphatase (PAP), also known as kallikrein-3 (KLK3), an over-expressed tumor antigen (Kantoff et al. 2010). Provenge is generated by isolating APCs and cultured with a PAP linked to GM-CSF. The approval of Provenge has inspired more efforts toward the development of similar therapies. However, what has become apparent is that the most effective form of vaccines against cancer would also act as preventive agents; although rather than protecting against malignancy, vaccines would be used to prevent relapse in minimal disease settings. The reason that this clinical setting seems better than the bulky cancer setting is that tumors alter many immunological components and environments, which directly hinders immune response to the vaccine, increases the tumor burden, and leads to lowered effectiveness of the vaccine (Nestle et al. 2005).

Strategies for Cancer vaccination

Identifying the right antigen, the right adjuvant, and the right immune responses are the common challenges facing cancer vaccination. Several types of vaccines have been proved to generate tumor-antigen-specific immunity including peptide, protein, whole tumor cells, DC, DNA, and viral, each with its own potencies and limitations (Nestle et al. 2005, Pijpers et al. 2005).

Peptide-based vaccines

A peptide cancer vaccine is kind of subunit vaccine in which a specific peptide of the complex tumor antigen is used for immunization. Tumor-specific peptides are identified based on binding capacity to specific molecules of HLA-I or II (Pijpers et al. 2005). The advantage of targeting the HLA class I, but not class II molecules, is that a high percentage

(up to 35–50%) of the population may carry a copy of individual HLA-I (Yaddanapudi et al. 2013). The peptides that bind to HLA class I enclose unique sequences, mounting the numbers of sequence that would need to be built into the vaccine with adequate population coverage. Studies have just shown that an individual HLA-DR peptide may bind to numerous HLA-DR subtypes (Disis et al. 2002). Therefore, it might take fewer HLA class II peptides, compared to peptides of HLA class I, to prepare a wide range vaccines. Despite protein vaccines, the greater cost benefits, ease of synthesis, formulation, and delivery are further advantages of peptide-based cancer vaccines. One probable difficulty with using specific peptide cancer vaccines is the occurrences of antigen-loss variants of tumor cells (Zhou et al. 2004, Sanchez-Perez et al. 2005). Polyvalent tumor antigens such as allogeneic whole tumor cell vaccines, which may minimize the risk of antigen loss variants and increase population coverage, seem to offer advantages when applied. (Yajima et al. 2005).

Whole tumor cell vaccines

Whole tumor cell vaccination is an effective procedure of injecting attenuated or killed tumor cells, usually along with costimulatory compounds such as cytokines (Parmiani et al. 2011, Li et al. 2007). The procedure falls under the three basic classes including autologous, allogeneic and gene-modified vaccines. In contrast to specific peptide vaccines, whole tumor cell vaccination allows for the immune system's natural ability to recognize most immunogenic TSAs, which obviates the need for MHC restriction-specific epitope identification. However, possible breakage in self-tolerance to normal molecules in the presence of costimulatory adjuvants might result in autoimmune responses. In a gene-modified approach, modification of inactive melanoma cells to secrete immunostimulatory molecules, such as GM-CSF, was shown to improve tumor antigen presentation through DC and macrophage-evident recruitment, production of tumor-specific $CD4^+$ and $CD8^+$ T cells, NKT-cells and antibodies for successful tumor rejection (Dranoff 2003). Autologous whole tumor cell approaches are currently being evaluated to treat acute myeloid leukemia and metastatic non-small cell lung carcinoma (Cheuk et al. 2006, Salgia et al. 2003).

Heat-shock protein vaccines

Heat-shock proteins (HSPs) carrying multiple undefined immunogenic tumor antigens can be purified from a patient's tumor cells and used as a polyvalent autologous cancer vaccine preparation (Srivastava 2005). The significance of HSPs in tumor antigen presentation and cross-presentation still remains undiscovered. Some reports agree on the opinion that HSPs can bind and present tumor antigens to APCs through HLA-I and II molecules, to activate tumor-specific $CD8^+$ and $CD4^+$ T cells (Srivastava 2005). The effectiveness of HSP vaccines lies in the ability of HSPs to concurrently serve as adjuvants and stimulate both innate and adaptive immune responses. Upon engagement of surface HSP receptors such as c-type lectin receptors and scavenger receptors, DC undergo a maturation process that enables them to become potent APCs (Binder et al. 2000). Potent immune responses and evident lesion regression was reported in a late phase II clinical trials using the Hsp7-HPV 16 fusion protein vaccine in women with advanced cervical cancer (Roman et al. 2007).

Anti-idiotypic antibody-based vaccines

Injection of tumor-specific mAbs may result in the formation of autologous antibodies against the original vaccine (Mocellin et al. 2004). The latter antibodies, known as anti-idiotypic antibodies, are specific for idiotopes of the original mAb. These antibodies, in an adjuvant combination, are used as a cancer vaccine (Rico and Hall 1989). An example of anti-idiotype cancer vaccine is Racotumomab. Racotumomab induces and targets immune response to a type of ganglioside, N-glycolil (NGc) GM3 (NGcGM3), expressed on the surface of lung, breast, melanoma tumor cells (Vazquez et al. 2012). An additional well-studied tumor antigen is the tumor-specific idiotype expressed on B cell lymphomas (Rico and Hall 1989). The vaccines studied are comprised of tumor-derived Ig containing tumor-specific idiotypes. The significance of anti-idiotypic vaccines is that it allows effective immunization against non-protein antigens, such as tumor-specific carbohydrate or lipid antigens, to draw an effective T cell memory.

Dendritic cell-based vaccines

DC therapy or DC vaccine is a recent, safe, and promising class of cancer treatment and prevention therapy even in advanced cancer patients who have failed all the possible therapies (Palucka and Banchereau 2013). As the most competent activators of naive T cells, taking DCs in cancer drugs to induce the effective tumor antigen-specific response makes great sense for tumor biologists (Palucka and Banchereau 2013, Steinman and Banchereau 2007). Several DC-based cancer vaccines have been developed to date, including DC loaded with tumor peptides or whole proteins (Li et al. 2000, Timmerman et al. 2002), DC pulsed with tumor antigen RNA or DNA (Boczkowski et al. 2000, Milazzo et al. 2003, Nencioni et al. 2003), DC transduced with viral vectors such as lentiviruses, retroviruses, fowlpox, adenoviruses and alphaviruses (Kim et al. 1998, Caley et al. 1997) whole-killed and protein extract of tumor cells (Galea-Lauri et al. 2004, Chen et al. 2001, Ferlazzo et al. 2000), and DC-fused with tumor cells using hybrid technology (Gong et al. 2000, Chen et al. 2000, Garcia-Marquez et al. 2013). Although DC-based vaccines have shown promising results in several preclinical and clinical settings, choosing the proper DC functional subpopulation with different functions and capacities is a great matter to deal with. Each functional subpopulation of DC has a unique capability of activating or suppressing different functional T CD4 + subsets (Feili-Hariri et al. 2005, Palucka and Banchereau 2013, Strioga et al. 2013).

DNA and viral vector-based vaccines

DNA vaccines are designed to produce an immunological response against certain antigens by injecting the genetically engineered DNA encoding corresponding antigens. DNA vaccination has unique advantages over other vaccination procedures, including the capability to induce a broad spectrum of immune responses, benefits afforded by their ease

of production and low cost, and the fact that the information pertaining to the HLA-I and II genotypes (Stevenson et al. 2004, Stevenson 2004) is not required. Similar to protein-based vaccines, DNA vaccines depend on antigen processing and presentation by APCs (Donnelly et al. 2005, Zhou et al. 2004). DNA vaccines are supposed to deliver a gene of particular tumor antigens to the body as a bacterial vector. The first demonstration of a plasmid-induced immune response was observed when mice inoculated with a plasmid-expressing human growth hormone elicited antibodies instead of altering growth (Tang et al. 1992). In practice, the infected host cells express the particular tumor antigen, drain into the lymph node, and eventually, after being taken up by DCs and presented to T cells or being recognized by B cells, trigger a broad range of immune responses (Yu and Finn 2006). In contrast to peptide-based vaccines that draw on a specific arm of immunity, DNA vaccines are characterized by activation of a broad spectrum of effector arms of the immune system (Zhou et al. 2005). The risk of integration with the host genome and thereby affecting genes controlling growth and survival, the possibility of antibody production against DNA, and the limitation to protein tumor antigen are downsides of DNA vaccines (Robinson and Pertmer 2000). However, application of RNA instead can obviate the possibility of integration (Hess et al. 2006, Heiser et al. 2000). DNA vaccine platforms can be made more immunogenic by inserting and encoding DNA into viral vectors. Live recombinant viral vaccines have been studied as cancer vaccines for years (Harrop and Carroll 2006). By mimicking a natural infection and offering the danger signals required for full activation of DC, viral vectors present a promising strategy for tumor antigen delivery (Draper and Heeney 2010). The first trial with viral vectors was vaccinia, over two decades ago (Mackett et al. 1982), and numerous viral vectors have been constructed on the poxviruses, such as avian poxviruses, fowlpox, modified vaccinia virus Ankara (MVA), canarypox, recombinant adenoviruses, and herpes virus (de Bruyn et al. 2004, Triozzi et al. 2005, Rosenberg et al. 1998).

Particle-based vaccine

Microparticles, emulsions, immune-stimulating complexes (ISCOM), liposomes, virosomes, and virus-like-particles (VLPs), are particulate vehicles for antigen that are increasingly being applied in vaccine formulations as carriers that deliver the tumor antigen to DC, in a much more immunogenic form. Particle platforms provide several advantages, such as sharing a similarity in size with the pathogens, and the capacity to carry multiple copies of the tumor antigen on the surface of the particle, which can be as effective as those internalized by DC, macrophages, and B cells (Newman et al. 2002, Randolph et al. 1999). Moreover, danger signals, and costimulators such as HSP and unmethylated CpG DNA, could be incorporated with the tumor antigens during formulation to boost the activation of DC and elicit optimal adaptive immune response (O'Hagan et al. 2006).

Combinational therapy

Although recent clinical approvals on protective and therapeutic cancer vaccines represent major milestones, the optimal achievement of cancer therapy will likely benefit from a combination of cancer vaccines with other immunotherapeutic and non-immunotherapeutic approaches such as mAbs, chemotherapy, radiation therapy, and surgery. It is assumed that following a cancer vaccine ('prime') with other immunotherapeutics and/or non-immunotherapeutics ('boost') may provide the best-in-class cancer therapy regimen (Finn 2008). Several preclinical and clinical settings for combinational therapy have emerged. Cytotoxicity of HER-2 specific T cells is increased against tumor cells pretreated with trastuzumab (zum Buschenfelde et al. 2002). It is assumed that the antibody causes the internalization and degradation of HER-2, resulting in increased presentation of HER-2-MHC and eventually greater activation and expansion of HER-2-specific T cells. Clinical trials are currently underway to test for potentially improved efficacy using this combination. Using agents and protocols to deplete or inhibit circulating Treg such as cyclophosphamide, anti-CTLA4, and CD25-targeted agents such as Denileukin diftitox-enhanced immune-based therapies (Phan et al. 2003, Zou 2005).

Targeting cancer stem cell

Accumulating evidence suggests that a biologically unique subpopulation of tumor cells with undifferentiated and stem cell-like properties lies behind the formation and progression of tumors (Schächinger et al. 2004, Wollert et al. 2004). These infrequent cells can be distinguished from the vast majority of tumor bulk cells by their exclusive ability to initiate and perpetuate the growth of a malignant cell population indefinitely (Nguyen et al. 2012, Schulenburg et al. 2010). They are widely named "cancer stem cells" or tumor-initiating cells (TICs). Actually, these biologically unique subsets of cells (CSCs) are named and defined by their demonstrated ability to regenerate, progressively growing the tumor. The growth consists of cells resembling those in the original tumor (self-replicating ability) (Sarry et al. 2011), as studied through serial transplantations in immunodeficient non-obese diabetic (NOD)/severe combined immunodeficient (SCID) mice.

The CSC concept places considerable significance on clinical cancer therapy, as it throws light on that current therapeutic strategies that are generally developed to target the cancer bulk rather the CSCs as the seed of tumors. Moreover it may explain the reason why many treatments seem to be effective primarily but fail later due to ineffectiveness of current therapies on the rarer and grossly invisible populations of CSCs, which remain safe and sound to re-initiate tumor formation (Bao et al. 2006, Chen et al. 2007).

On the whole, this study emphasizes that the ultimate goal in the treatment of cancer is elimination of CSCs. To date, most efforts have focused on targets specifically expressed in CSCs, to develop new strategies for CSC elimination. Targeting surface molecules was the first that struck us as being a sensible strategy to distinguish CSCs from bulk tumor cells. However, surface molecules are expressed on the normal stem cells of the tissue as well, heightening the necessity of identification of more specific molecules that

Table II. Targeting cancer stem cells (CSCs) using immunotherapy.

	Mechanism of action	Tested leukemia or solid tumor	Ref.
Cancer stem cell mAb therapy			
Anti CD44	CD44 play pivotal role in LSC*-niche interactions	Human AML, breast cancer, head and neck cancer, and melanoma	159
Anti CD47	CD47 is overexpressed on LSCs to evade macrophage killing	Human AML LSCs	160
Anti CD27	CD27 signaling activates the canonical Wnt pathway, leading to LSC proliferation	CML** LSC	161
Anti IL-3Rα conjugated with Indium111	Delivering radioactive compounds and resulting in DNA double strand breaks	AML LSCs	162
Cancer stem cell cellular therapy			
Minor histocompatibility-specific CTLs and NK cells	Graft versus leukemia (GVL)	AML LSCs	163
Donor lymphocyte infusions (DLIs) in combination with imatinib	Block LSC engraftment	Murine CML	164
Forcing CSCs into the cell-cycle by breaking their dormancy			
CML patients treated with imatinib and IFN-α	IFN-α induce proliferation of CSCs and make them more sensitive to DNA damage-inducing chemotherapeutics	CML	157

*Leukemia stem cells (LSCs), **Chronic myelogenous (or myeloid) leukemia (CML).

are exclusively expressed on CSCs (Jordan et al. 2006, Essers and Trumpp 2010).

$CD133^+$ cancer cells of the brain, colon, lung, and pancreas, $CD44^+CD24$low or $CD44^+CD24^-$ human breast cancer cells, $CD47^+$ bladder, $CD90^+$ liver, ABCB5+ (ATP-binding cassette sub-family B member 5) of melanoma and $CD34^+CD38$low or $CD34^+CD38^-$of many human AML cancer cells are well characterized and accepted as CSCs (Taussig et al. 2008, Nguyen et al. 2012, Riether et al. 2013).

Immunotherapy is now considered to be a reasonable strategy to directly attack CSCs and eradicate quiescent CSCs. Candidates for immunotherapy of CSCs include CSCs mAb therapy, activated cytotoxic CD8 + T cells (CTLs), and NK cells specific for CSCs; another possibility is to force CSCs into the cell-cycle by breaking their dormancy, followed by conventional cytotoxic chemotherapy (Table II) (Riether et al. 2013).

Declaration of interest

The authors report no declarations of interest. The authors alone are responsible for the content and writing of the paper.

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