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REVIEW

Therapeutic cancer vaccine: building the future from lessons of the past

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Abstract
Anti-cancer vaccines have raised many hopes from the start of immunotherapy but have not yet been clinically successful. The few positive results of anti-cancer vaccines have been observed in clinical situations of low tumor burden or preneoplastic lesions. Several new concepts and new results reposition this therapeutic approach in the field of immunotherapy. Indeed, cancers that respond to anti-PD-1/PD-L1 (20–30%) are those that are infiltrated by anti-tumor T cells with an inflammatory infiltrate. However, 70% of cancers do not appear to have an anti-tumor immune reaction in the tumor microenvironment. To induce this anti-tumor immunity, therapeutic combinations between vaccines and anti-PD-1/PD-L1 are being evaluated. In addition, the identification of neoepitopes against which the immune system is less tolerated is giving rise to a new enthusiasm by the first clinical results of the vaccine including these neoepitopes in humans. The ability of anti-cancer vaccines to induce a population of anti-tumor T cells called memory resident T cells that play an important role in immunosurveillance is also a new criterion to consider in the design of therapeutic vaccines.

Keywords Cancer vaccine · Checkpoint inhibitor · Tumor antigens · $CD8^+$ T cells · Resident memory T cells · Therapeutic combination

Introduction

Anti-cancer vaccines began to develop with the identification of tumor-associated antigens in the early 1990s [1]. Despite some clinical successes and a cancer vaccine approved in prostate cancer patients [2], their clinical position in cancer therapy remains limited. The recent emergence of new immunotherapeutic strategies based on blocking inhibitory checkpoints (anti-PD-1/PD-L1, anti-CTLA-4) or cellular therapy by CAR T cells tends to marginalize anti-cancer vaccines in this therapeutic field. Nevertheless, a better understanding of the mechanisms of resistance to these vaccines, the need for a preexisting immune response for the success of PD-1/PD-L1-blocking antibodies, and the identification of mutated tumor antigens as novel targets for vaccine foster new clinical development of cancer vaccines [3].

The right choice of tumor antigens in the design of cancer vaccine

The aim of cancer immunotherapy is to stimulate the immune system against tumors cells while preserving normal tissues. Tumors express antigens that could be recognized by the immune system. Humoral and cellular immune responses to tumor-specific antigens, either spontaneously or vaccination-induced, have been detected in cancer patients [4].

The first tumor antigen recognized by T cells, MAGE-A1, was discovered in 1991 [1, 5], and many more tumor antigens have been identified since then [4].

Tumor antigens can be classified according to their expression and localization, and two main categories of tumor antigens can be distinguished: tumor associated antigens (TAA) and tumor specific antigens (TSA) (Fig. 1).

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	TAA : Tumor associated antigen			TSA : tumor specific antigen	
Antigen category	**Differenciation antigen**	**Overexpressed antigen**	**Cancer testis antigen**	**Oncogenic virus-derived antigen**	**Mutated antigen (neoantigen)**
Description	Expressed on tumor cells and normal cells originate from the same tissu	Expressed on normal cells at low levels Overexpressed on tumors cells	Normally expressed in germs cells but aberrantly expressed in tumor cells	Absent in normal cells Arise from ongenic viral protein	Absent in normal cells Arise from somatic mutation
	Can be subject to central tolerance			Not subject to central tolerance	
Location of expression	Mart1, gp100 in melanomas PSA, PAP in prostate cancers	Her2/neu in breast and ovarian cancers, kidney carcinomas MUC1 in lung and breast adenocarcinomas	MAGE-3 in melanoma, bladder cancers NY-ESO1 in melanomas and ovarian cancers	HPV oncoproteins E6 and E7 in HPV associated head and neck and gynecologic cancers HBs Hepatitis B virus in hepatocarcinoma	P53 mutations in various cancer RAS mutations in various cancers Bcl-Abl fusion protein in leukemia
Examples of cancer vaccines targeting the antigen	Prostate cancer : Sipuleucel-T : autologous DC-based vaccine against PAP, approved in US and in Europe (2)	Overexpressed Her2/neu breast and gastric cancers : Trastuzumab, anti Her2/neu monoclonal Ab, associated with chemotheray	NSC lung cancer : vaccination with MAGE-3 protein, MAGRIT (phase 3 trial)(15) Melanoma and sarcoma : adoptive transfert of autologous T cells transduced with NY-ESO1 TCR (12)	HPV associated cervical intraepithelial cancer : VGX-3100, synthetic plasmide coding for HPV16-18 E6 and E7 proteins, (phase 2b trial) (130)	Melanoma : vaccination with synthetic RNAs coding for mutated peptides (phase I trial) (35) vaccination with neopeptides (Phase I trial) (34)

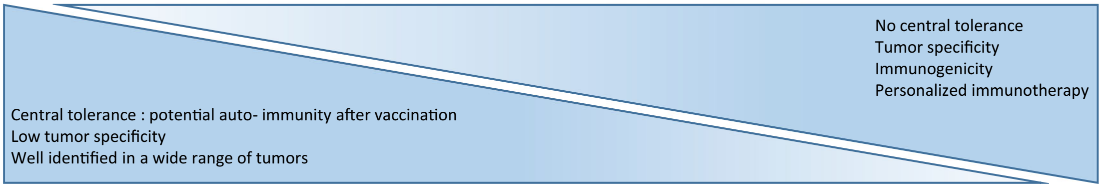

Fig. 1 Tumor antigens: main characteristics

TAA are expressed in normal cells and include differentiation antigens, overexpressed antigens, and cancer testis antigens. Many studies have shown that TAA are immunogenic and are able to induce specific T cells [6]. Differentiation antigens are expressed only in tumor cells and in the healthy tissue of origin; for example, the prostatic specific antigens (PSA) and prostatic acid phosphatase (PAP) are found in normal prostate and in cancer prostate, and MART1/Melan-A in normal melanocytes an in melanoma. Sipuleucel-T, an autologous DC-based immunotherapy targeting PAP, was the first FDA-approved cancer vaccine for metastatic castration-resistant prostate cancer [2]. Tumors cells can also overexpress proteins, which are normally expressed at low levels in healthy cells (e.g., Her2/neu, TERT (telomerase), survivin). Some of these overexpressed antigens, such as Her2/neu in ovarian, breast, and gastric cancers, can directly participate in the oncogenic process by promoting growth and survival of tumor cells. Overexpressed proteins in tumors are potential targets, and may provide a T cell specific response, as a threshold level of antigen is required for presentation and recognition by T cells. Immunotherapies targeting the overexpressed antigen Her2/neu have proven clinically efficacy. The anti-Her2/neu monoclonal antibodies (trastuzumab, pertuzumab) are approved for the treatment of Her2neu overexpressed breast and gastric cancers [7]. Moreover, many clinical trials using peptides or proteins derived from Her2neu induce cytotoxic antigen-specific T cell responses in metastatic breast cancer [8, 9].

Cancer testis antigens are normally expressed in germ cells (testis, fetal ovaries), whereas they are aberrantly expressed in various tumors such as lung or bladder cancers and in melanoma [10]. Many cancer testis antigens have been identified like MAGE family antigens or NY-ESO1. These antigens are more attractive targets for immunotherapy than the previous one due to their restricted expression in tumor cells despite their expression in germ cells, as these cells do not express MHC molecules, thus precluding antigen presentation to T cells [11].

In many clinical studies, the targeting of these antigens in melanoma, lung or ovarian cancer, elicits antigen-specific $CD4^+$ and $CD8^+$ T cell responses. However, despite their demonstrated immunogenicity, they were not associated with clinical benefit [12–15].

So, TAA are attractive targets in cancer immunotherapy as they are shared antigens across many tumors able to elicit specific T cell and humoral responses. However, as TAA are expressed in normal cells, specific mechanisms of tolerance may have occurred for some of them. In some cases, secondary to the negative thymic selection of self-antigen, these TAA elicit low avidity rather than high-avidity T cells. Interestingly, some TAA antigens such as hypoglycosylated MUC1 are abnormally expressed during some acute viral infection such as in mumps and trigger an immune response. It has been shown that a history of childhood mumps may protect against ovarian cancer [16].

In contrast to TAA, TSA are not expressed in normal cells. They arise either from oncogenic viral proteins in virally induced cancer, or from somatic mutations of normal proteins (neoantigens) or result from neoepitope generated by translocation or aberrant splicing of normal proteins.

TSA are the more attractive immunotherapy targets, as they are perceived as foreign antigens by the immune system. Therefore, they are not susceptible to central tolerance. Using TSA as targets leads to safer, more specific, and more effective vaccine, as there is fewer risk of side effects in healthy tissues and because they elicit higher avidity specific T cells than those generated with self-antigens [17, 18].

Viruses-derived antigens have been identified in virus-induced cancers such as HPV-associated cancers (head and neck cancers, cervical cancers, anal cancer…) or hepatitis B virus-associated hepatocellular carcinoma. Vaccination of the whole population of Taiwan with recombinant hepatitis B vaccine decreases the frequency of primary hepatocarcinoma [19, 20]. In HPV-associated cancer, vaccination using these antigens has been successful with the first approved prophylactic vaccine Gardasil® and cervarix leading to the decrease of the prevalence of cervical intraneoplasia in young women in some countries with good coverage of the vaccine in the teenager [21, 22]. Neoantigens are generated during cancer initiation and progression, where tumor cells acquire mutations due to genomics instability and altered DNA repair machinery. Some tumor types present a great number of somatic mutations due to exposure to mutagen agents: lung cancers and tobacco [23], melanomas and UV radiation [24], and all cancer with high microsatellite instability and mismatch repair deficiency [25]. Some mutations can drive oncogenesis in tumors cells (driver mutations), while others have no effect or are not involved in oncogenesis (passenger mutations) [26].

Many studies have shown that neoantigens are highly immunogenic [27–30] and spontaneous neoantigen-specific T cells have been detected in cancer patients [31].

Now combining genomics and bioinformatics with an immunological approach enables to rapidly identify, in only few weeks, several neoantigens that can bind to a given HLA molecule [32, 33].

However, mutations must lead to presentation of the identified mutated peptide and a T cell repertoire has to be present for these neoantigens. Results from mice reported than from 1000 mutations identified, only 10–40 appear to be immunogenic.

Recent clinical trials with personalized neoantigen vaccines (DC-based vaccine, long neopeptides, or synthetics RNA coding for neopeptides) have been able to induce effective T cell response and provide some clinical benefits in melanoma after vaccination [34–36].

These studies confirm the feasibility of personalized neoantigen vaccine, although developing a personalized vaccine will likely be more expensive and more time consuming than developing a conventional vaccine.

More recently, other types of molecules not expressed by tumor cells but rather by protumor cells such as fibroblasts or endothelial cells, like VEGF, or immunosuppressive molecules have been introduced in cancer vaccine with encouraging clinical results [37–40].

From these data, some rules emerge for the selection of tumor antigen. The frequency and the distribution (homogeneous or heterogenous) of the tumor antigen have to be considered. Tumor antigen which expression is required for cell survival has to be privileged. Non-self-antigens (viral antigens, neoantigens (mutated antigens), may be preferentially selected due to their higher immunogenicity and higher ability to elicit high avidity T cells than self-antigens, and their decrease risk of generating autoimmunity. In that context, targeting neoantigens from driver mutations may be more relevant, as these mutations are most likely essential for tumor oncogenesis. In rare cases, public neoantigens with hot spot mutations, such as the H3.3K27M mutated peptide restricted by HLA-A*02:01 in gliomas or the KRAS G12D or G12V mutated peptide restricted by HLA-C*08:02 or HLA.A*11:01, respectively, in colorectal cancer, lung cancer, or pancreatic cancer, as well as the CDK4 R24C or R24L mutated peptide restricted by the HLA-A*02:01 alleles have been described [41]. They represent particularly attractive antigens to be selected in cancer vaccines. Clinical trials targeting these antigens are ongoing (NCT03190941, NCT02960230).

$CD8^+$ T cells: the main anti-tumor effector cells in vaccine efficacy

The rational of therapeutic anti-tumor vaccine is supported by the fact that adaptive immune system, which is highly involved in tumor control, is impaired in cancer patients but can be restored and amplified by vaccination. Among all immune cells, it is well known that $CD8^+$ T cells plays a crucial role in tumor control. Indeed, they display a large specter of cytotoxic mediators in response to the specific recognition of tumor antigen and MHC class I complex. They favor tumor cell death by direct or indirect manners: the release of lytic molecules, the binding to pro-apoptotic receptors expressed by tumor cells, the secondary recruitment of effector cells, or the increase of tumor cell recognition via the induction of MHC-I molecules. Such high cytotoxic capacities make their induction and infiltration into tumor an attractive therapeutic challenge.

In mice, compelling studies correlate the levels of CD8$^+$ T cells induced after cancer vaccine and tumor regression [42].

Supporting these results, various murine models show that the depletion of CD8$^+$ T cells by monoclonal antibody results in the loss of tumor inhibition observed after cancer vaccine administration, demonstrating the crucial impact and need of CD8$^+$ T cell induction [43, 44].

In human, a correlation has been reported between CD8$^+$ T cell response in vaccinated patients and clinical response and overall survival [45–47].

In addition to these statements, it is necessary to underline that anti-tumor therapeutic vaccination has to generate not only tumor-specific CD8$^+$ T cells but also tissue-resident memory T cells (TRM) at the tumor site. Indeed, recent studies show that TRM are emerging as an essential actor involved in tissue immunosurveillance by their specific expression of adhesion molecules (CD103 or CD49a integrins, chemokine receptors) facilitating their retention into tissues and consequently into tumor. Their well-positioned location in close contact with tumor cells and their higher cytotoxic capacities explain that their tumor infiltration is correlated with good clinical outcomes in many cancers [48]. Accordingly, it appears that eliciting TRM represents a novel grail for the success of cancer vaccine.

Our group demonstrated the role of TRM in vaccine efficacy using various strategies. The depletion of TRM using an antibody against CD49a integrin or the co-administration of anti-TGFβ—which block TRM differentiation—with cancer vaccine hampers tumor growth control by the vaccination. The FTY720 pharmacologic blockade of effector T cell recruitment from lymphoid organs to tissue and the employment of parabiosis experiments, which allow the distribution of circulating but not of TRM T cells between the two mice, revealed the efficient anti-tumor role of TRM alone, without the help of effector T cells [49].

In line with these results, in human, the induction of specific TRM-like CD8$^+$ T cells expressing the VLA-1 or $\alpha 1\beta 1$ integrin (where $\alpha 1$ corresponds to CD49a) correlated with a better survival of patients vaccinated with the overexpress tumor antigen Melan-A [50]. Even though, it should be noticed that both effector and TRM CD8$^+$ T cells are needed to elicit a potent immune response [51].

The crucial role of the intratumoral CD8$^+$ T cells has been recently reported in studies aiming to elucidate the mechanisms of the Sipuleucel-T cancer vaccine approved for metastatic prostate cancer patients. Indeed, the authors did not found the presence of CD8$^+$ T cells against the PAP-targeted vaccine in the blood, but they were present in the nest of the tumor with a phenotype of activated T cells [52]. It reminds previous results with autologous tumor-cell vaccination, in which the presence of circulating anti-tumor CD8$^+$ T cells was not correlated with clinical response, while specific anti-tumor intratumoral CD8$^+$ T cells were associated with a better survival in melanoma patients [53].

This predominant role of intratumoral CD8$^+$ T cells could explain the absence of association in some clinical studies between the levels of CD8$^+$T cells in the blood and clinical response [54, 55].

Antigen spreading which corresponds to secondary CD8$^+$ T cells response against antigen not present in the vaccine likely due to an antigen release after the first wave of CD8$^+$ T cell directed against the tumor provide additional evidence for the role of these effector cells. Indeed, in human clinical case studies, it was reported that the tumor regression may be dependent on CD8$^+$T cells directed against tumor antigens not present in the vaccine [56–58].

Taken together, the induction of CD8$^+$ T cells might be a suitable surrogate biomarker based on immune-related response criteria to evaluate therapeutic anti-tumor vaccine. However, the intratumoral localization of these CD8$^+$ T cells may be critical for the success of cancer vaccine.

Current promising strategies to induce anti-tumor CD8$^+$ T cells

Although the induction of CD8$^+$ T cells represents the main goal of cancer vaccine, the ability to elicit these cells at high levels in cancer patients remains a failure. In the literature, very few patients exhibited ex vivo CD8$^+$ T cell response after cancer vaccine administration [59–61]. In the great majority of clinical trials including neoantigen-targeted vaccines [34, 35], the need of in vitro amplification of T cell response is required [62–67], suggesting that the strategies used to elicit CD8$^+$ T cells in humans need to be improved.

The principle of vaccination is inspired by viral infection process which is triggered by the recognition of specific motifs (PAMP) by PRR (pattern recognition receptor) of APC (antigen-presenting cell) followed by virus internalization and APC maturation to finally allow cross-presentation of derived peptides via MHC-I molecules to naïve CD8$^+$ T cells and provide sufficient activator signals (Fig. 2).

Signals to favor DC maturation

One of the most critical time points to efficiently prime naïve CD8$^+$ T cells relates to their contact with mature DC. Mature DCs are recognized as the only cells able to prime naïve CD8$^+$ T cells while immature DCs promote CD8$^+$ T cell anergy. The use of vaccine endowed with the

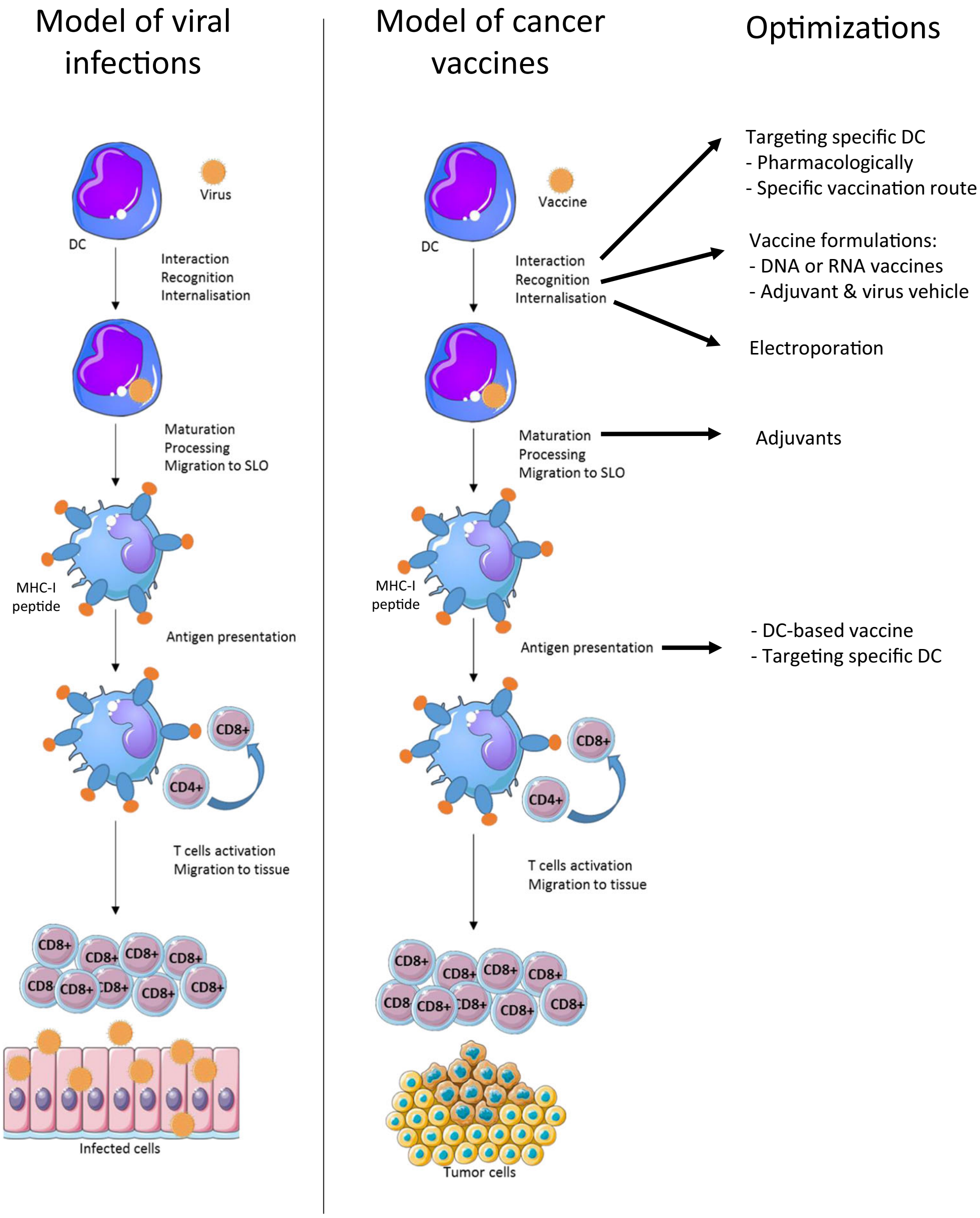

Fig. 2 Promising strategies for cancer vaccines. Cancer vaccine is based on the model of viral infection, where the dendritic cell (DC) interacts, recognizes, and internalizes the virus. This leads to the matiuration, the processing of the derived viral peptides and the migration of the DC to the secondary lymphoid organs (SLO). In the SLO, the DC presents the MHC class I (MHC-I) peptide complex to CD8+ T cells which conduce to their activation, amplified by CD4+ T cells, and then to their migration to infected tissue. Promising strategies are developed in the right part of the figure

properties to favor DC maturation has been developed. Some vaccine formulations including DNA, RNA, or DC-based vaccines naturally exhibit direct immunostimulatory properties and have been shown to elicit CD8$^+$ T cells in mice and in humans [68]. However, in the last setting, the induction of CD8$^+$ T cells is low and required in vitro stimulation. Some discrepancies between results obtained in mice and humans especially for DNA vaccine have to be more explored [69].

The use of adjuvants with immunomodulatory properties is largely appropriate to favor DC maturation [70] (Fig. 2).

Direct immunostimulatory adjuvants such as TLR (toll-like receptor) or CD40 agonists, cytokines, or activators of IFN genes are indicated to potentiate vaccine immunogenicity and avoid self-TAA tolerance. Interestingly, some adjuvants can also preferentially polarize the immune cells to a Th1 response with CD8$^+$ T cells. In a murine model, it has been shown that TLR agonists and especially Poly:IC (TLR3 ligands) or CpG (TLR9 ligands) mixed or not with montanide reproducibly elicit CD8$^+$ T cells in mice and in human [71, 72]. Interestingly, CpG and Poly:IC increased the ratio between effector CD8$^+$ T cells and regulatory T cells (Treg) [73]. Stimulator of IFN genes (Sting) delivered via particle platform to reach the cytosol also favor the induction of CD8$^+$ T cells [74]. Although adjuvants show promising results to favor vaccine efficacy, at this time, only few immunostimulants have been approved for human use but several ones are currently tested in clinical trials.

Strategies to favor cross-presentation

When proteins based vaccine are internalized in the cell, they follow an intracellular traffic routing them into lysosomes, where they are degraded into peptides that associate with HLA class II molecules. This complex is presented to CD4$^+$ T cells, but not CD8$^+$ T cells.

Some subpopulations of DC could direct extracellular protein in the MHC class I pathway, and this process is called cross-presentation.

Among all the different vaccine formulations, one of the most promising strategies uses recombinant attenuated live vectors derived from virus or bacteria as a vehicle for tumor antigen. Because of their intrinsic properties to reach the cytosol of the cells, these recombinant pathogen-derived delivery systems favor MHC class I restricted peptide presentation and induce a better CD8$^+$ T cell response than free proteins or peptide vaccines [75, 76]. In addition, they are endowed with a natural immunogenicity as they express PAMP and can be engineered to also express activating molecules like cytokines (IL-2) or immunomodulatory molecules (B7.1; a trial of costimulatory molecules called TRICOM: B7.1, ICAM-1, and LFA-3) to further amplify vaccine response [77].

However, it has to be reported that live vectors cannot be administrated repeatedly: a diversified prime-pull strategy using distinct attenuated pathogens is required to overcome the bacteria or virus neutralization by host immunity.

Several non-replicating live vectors have been tested in clinical trials and shown minimal toxicity with good ability to generate CD8$^+$ T cells [78, 79]. Other vehicles such as emulsions, liposomes, virosomes, or nanoparticles [80, 81] can also favor cross-presentation to CD8$^+$ T cells in parallel to delivering immune signals. They were efficient in mice, but no convincing data were yet shown in humans.

Short CD8$^+$ peptides can bypass the need of cross-presentation by directly binding to MHC-I molecules, but they show low efficiency due to the lack of CD4$^+$ T cell help, demonstrating consequently the interest of cross-presentation. Various groups in preclinical models showed that long peptides encompassing both CD8$^+$ and CD4$^+$ epitope successfully elicit antigen-specific CD8$^+$ T cell response in mice and in humans [82, 83]. However, in the latter setting, the immune response was mainly composed of CD4$^+$ T cells [84].

Targeting DC

Actually, cross-presentation is restricted to specific DC subpopulations and especially CD141$^+$ DC designed as cDC1 [85]. Recent studies revealed that antibody-based vaccination directed against specific DC receptors allow a better antigen load to presenting DC and enhance anti-tumor vaccine efficiency in an optimal manner [86]. This approach is based on the fusion of tumor antigen with a protein, which delivers the immunogen to DC in situ. As an example, our group was the first to demonstrate that targeting DC in vivo with the B subunit of Shiga toxin (STxB), a non-toxic vector, which binds to Gb3 preferentially expressed by DC, significantly increased the number of antigen specific CD8$^+$ T cells when coupled to various antigens [87–89]. From this pioneer study, various cancer vaccines targeting various molecules preferentially expressed on DC have been developed (DEC-205, Clec9a/DNGR, XCR1, CD11b…) [90–92]. Human studies using antibodies against DC receptors such as DEC-205 and Clec9a coupled with model antigens also reported an increase of cross-presentation resulting in significant induction of CD8$^+$T cells [93, 94].

Of course the sensitization of DC with tumor antigen in various formulation could also be administered as cancer vaccine as a cell therapy product [95]. However, the subpopulation of DC to be selected, the maturation signal to be used, and the formulation of antigen remain a matter of debate. However, this type of cancer vaccine has been shown to induce specific CD8$^+$ T cells but with no clinical impact [63].

How to induce local anti-tumor CD8$^+$T cells (TRM)

Many studies have reported in infectious contexts that only local vaccination allows the induction of TRM due to the imprinting of a molecular homing program induced by a specific local DC [96]. In line with these observations, in a head and neck orthotopic tumor model, our group showed that only mucosal (intranasal) and not systemic (intramuscular) vaccination with STxB coupled to E7 protein from HPV16 elicits an efficient tumor control through the induction of CD103$^+$ CD49a$^+$ CD8$^+$ T cells (TRM) [97]. Another study demonstrated the benefit of a cervico-vaginal boost with an HPV vaccine rather than a systemic intramuscular boost to elicit intratumoral CD103$^+$ TRM cells and better protect mice from a cervical tumor challenge [98]. Better understanding of the initial step of CD8$^+$ T cell priming, the complexity of DC subsets, specie differences, and the homing program to favor migration of induced CD8$^+$ T cell at the local tumor site still remain an interesting challenge for the optimal induction of CD8$^+$ T cells [99].

Non-CD8$^+$ T cell mechanisms mediating the efficacy of cancer vaccine

Besides the role of CD8$^+$ T cells, accumulative evidence support that some cancer vaccines elicit CD4$^+$ T cells mediating tumor regression.

It is acknowledged that CD4$^+$ T cells and especially the TH1 subpopulations have a key role in cellular immunity by their “helper” function [100, 101]. Activation of CD4$^+$ T cells is essential for optimal CD8$^+$ T cell priming, by enhancing antigen presentation and favoring cross-priming of tumor antigen by DC [100]. $CD4^+$ T cells also support recruitment of $CD8^+$ T cells to the tumor site [102], maintenance, and expansion of a $CD8^+$ T cell memory response [103–106]. Besides their "help" to $CD8^+$ T cell responses, $CD4^+$ T cells can mediate other anti-tumor effects: direct killing of tumor cells [107], recruitment and activation of innate immune cells (e.g., NK cells or type I macrophages) to the tumor site [108], and modulation of the tumor microenvironnement by an anti-angiogenic effects [109]. $CD4^+$TH1 cells also promote vessel normalization leading to better intratumoral $CD8^+$ T cell infiltration [110]. Adoptive cellular transfer (ACT) of specific anti-tumor $CD4^+$ T cells led to tumor regression in xenograft tumor models and in patients with cancers [111–113]. In addition, spontaneous or vaccine-induced $CD4^+$ TH1 response against specific-tumor antigens correlated with better survival in human [114–116]. In various tumor models, nonsynonymous cancer mutation preferentially led to the induction of $CD4^+$ T cells mediating tumor regression [117, 118]. In mice, depletion of $CD4^+$ T cells abrogated, totally or partially, the efficacy of cancer vaccine [119, 120].

Melanoma patients who were vaccinated with helper peptides present a stronger $CD4^+$ and $CD8^+$ T cell response and better clinical results, than those vaccinated with $CD8^+$ peptide alone [121, 122]. These results confirm that to elicit optimal anti-tumor responses, vaccines should activate both $CD4^+$ and $CD8^+$ T cells [123]. Nevertheless, it is important to mention that after therapeutic vaccine administration, both effector and regulatory $CD4^+$ T cells could be elicited and these latter cells could limit vaccine efficacy [124, 125].

Failures and success of therapeutic vaccine in humans

There is a long list of disappointed hopes following the administration of anti-cancer vaccines as monotherapy agent. The majority of phase 3 clinical trials did not confirm encouraging preliminary results in early clinical trials. These trials used different vaccine strategies, such as recombinant proteins (Mage A3, idiotype), tumor antigen-pulsed DC, recombinant viruses, $CD8^+$ peptides, or lipopeptides [3, 54, 126–129].

Fortunately, one cancer vaccine, Sipuleucel-T, an autologous DC-based immunotherapy targeting prostatic acid phosphatase, was approved by the FDA in metastatic castration-resistant prostate cancer [2, 130]. How to explain these failures and what are the avenues to explore to improve these anti-cancer vaccines?

The most documented explanation is that in the majority of cases, these anti-cancer vaccines have been used in very advanced and metastatic cancers, where the mechanisms of immunosuppression are dominant. Indeed, as a monotherapeutic agent, cancer vaccine has demonstrated its efficacy in metastatic cancer prostate patients, but with low tumor burden [2]. In addition, a DNA vaccine encoding the E6 and E7 proteins of oncogenic HPV types 16 and 18 was tested during a double-blind phase IIb clinical trial in patients with preneoplastic cervical lesion grades 2 and 3. In comparison with the placebo group, the vaccinated women had an increased frequency in the regression of their lesions and a decrease viral load [131]. In line with these results, the group of Melief and Van der Burg reported clinical activities of long peptides derived from HPV-E6 and E7 proteins in women with grade 3 intraepithelial neoplasia [132]. Interestingly, the same cancer vaccine did not induce tumor regression nor prevented the progression of the disease in more advanced stages [133]. More recently, the group of Czerniecki showed that in a neoadjuvant trial, Her2 peptide sensitized DC was more efficient to generate pathologic complete response in Her2-positive ductal carcinoma in situ than in Her2-positive invasive breast cancer [134]. From these previous clinical results, it appears clearly that cancer vaccine as monotherapeutic agents should be abandoned in advanced metastatic disease, but only assessed in preneoplastic lesions or carcinoma in situ.

In addition, since many immunosuppressive mechanisms present in the tumor microenvironment (Treg, myeloid-derived suppressive cells, immunosuppressive molecules (IDO, IL-10, TGFβ)) will blunt the functionality of vaccine-induced $CD8^+$ T cells, combination of cancer vaccine with molecules with the ability to thwart immunosuppression appears as a prerequisite for the next generation of cancer vaccines.

Combination of cancer vaccines with molecules reversing immunosuppression or potentiating their activity

Combination of cancer vaccines with conventional drugs

Since chemotherapy, radiotherapy, and anti-angiogenic molecules can inhibit some mechanisms of immunosuppression, these drugs have been combined with cancer vaccines in preclinical models and in humans.

The groups of Melief and Van Der Burg reported that chemotherapy based on carboplatin and paclitaxel reduced myeloid suppressive cells in advanced cervical cancer patients allowing an enhanced immune [135] and clinical response [136] following cancer vaccine administration.

Radiotherapy could induce immunogenic cell death, the release of cytokines and chemokines, and vessel normalization leading to a permissive tumor microenvironment for immunotherapy. However, radiation could also increase the expression of PD-L1 and favor the recruitment of Treg and M2 macrophages. The global effect depends on the dose and sequence of radiotherapy [137]. We and others showed that radiotherapy synergized with cancer vaccine partly due to a better infiltration of vaccine-induced $CD8^+$ T cells secondary to vessel normalization [138].

Lastly, as expected, anti-angiogenic molecules, which reverse some immunosuppressive mechanisms in the tumor microenvironment, enhance the therapeutic efficacy of cancer vaccine [139].

Combination of vaccine with antagonist of inhibitory receptors or agonist of costimulatory molecules

Regulatory T cells which are increased in cancer patients may constitute a resistance mechanism to the efficacy of cancer vaccine [140]. In murine models, it has been reported that anti-CTLA-4 depleted activated Treg which express this molecule in the tumor microenvironment [141, 142], while anti-OX40 inhibit the suppressive activity of Treg [143, 144] and anti-GITR allow $CD8^+$ T cells to be more resistant to their blockade mediated by Treg [145].

Our group and others have reported an induction of checkpoint inhibitors after cancer vaccine administration [146, 147]. In addition, immune checkpoint inhibitor efficacy seems to depend on preexisting intratumoral $CD8^+$ T cells underlining the necessity to induce these cytotoxic T cells with vaccination [148, 149].

These results constitute a strong rationale for the combination of cancer vaccine with antagonist of checkpoint inhibitors or agonist of costimulatory molecules.

In preclinical models, the combination of checkpoint blocking antibodies (anti-CTLA-4, anti-PD-1/PD-L1) with cancer vaccine based on peptide, recombinant live vectors, DNA, DC, or autologous tumor cells increase the vaccine-induced immune and clinical response [150]. The formulation of the vaccine, especially in the non-persistent format of the vaccine, seems to be critical for the efficacy of this combination [151].

Although most combinations used anti-CTLA-4 or anti-PD-1-PD-L1, the blockade of other inhibitory receptors (Lag3, Tim-3, Vista…) has demonstrated some synergy with cancer vaccines [152–154]. Various costimulatory molecules belonging to the TNFR family (CD40, OX40, 4-1BB (CD137)…) have been targeted by agonist antibodies in combination with cancer vaccines resulting in increased immunogenicity of the vaccine and tumor potency [155–160].

Combination of antagonist antibodies (anti-PD-1 and anti-CTLA-4) [161, 162] or a mixed of antagonist and agonist antibodies (anti-CTLA-4 and anti-CD40 or anti-OX40, anti-PD-1/PD-L1 with anti-CD40 or anti-4-1BB…) further increased the efficacy of cancer vaccine [163–168] likely due to possible co-expression of checkpoint inhibitors on $CD8^+$ T cells [169].

In humans, anti-CTLA-4 combined with peptide vaccine did not lead to increased clinical response in melanoma patients [170–172]. Clinical results were more encouraging when more complex cancer vaccine based on dendritic cells or recombinant virus was combined with anti-CTLA-4 mAb [173–175].

Results from the combination of cancer vaccine with the blockade of PD-1-PD-L1 axis are very scarce. One did not support the synergy of this combination [176], while others reported a possible synergy when compared to historical control cohorts [177, 178].

Conclusions

Because of past failures of anti-cancer vaccines and at the era of successful therapeutic activity of checkpoint inhibitor blockade, one may wonder if vaccine still has a future. It can be argued that only 20–25% of the patients treated with drugs targeting checkpoint inhibitors have a clinical benefit and one cue to improve these treatments is to induce an anti-tumor $CD8^+$ T cell response for which cancer vaccine remains competitive.

What should we improve in the cancer vaccine previously developed to lead them to clinical success? The intrinsic design and composition of cancer vaccine have to be revisited. The use of non-self-antigens (mutated antigen) should improve their immunogenicity. Many biotech companies targeting neoepitopes have emerged in the last years giving a revival in the cancer vaccine field.

Not only the number of vaccine-induced $CD8^+$ T cells but also their persistence and their localization should constitute novel criteria for the design of potent cancer vaccine. Prolonging antigen presentation by using some delivery systems such as the B subunit of STxB or repeated injection of peptide increase the number of long-lasting $CD8^+$ T cells [179, 180]. In many past cancer vaccines, the induction of $CD8^+$ T cells were transient [181, 182]. Mucosal route of immunization should be assessed to favor the induction of resident memory $CD8^+$ T cells [48]. Various effector arms of the innate and adaptive immune system should be engaged to eradicate large established tumors [183].

For the combined therapy, there is yet no criteria to select the blockade pathway (CTLA-4-CD80-CD86, PD-1-PD-L1/2) or the costimulatory pathway (CD40; OX40, 4-1BB) which should be engaged with cancer vaccines. In mice, one study compared a peptide vaccine with various inhibitory or stimulatory antibodies and found that anti-4-1BB was superior to other antibodies, when combined with peptide vaccine [155].

The timing of combination therapy is likely a critical point that is rarely addressed in clinical trials. Some rules emerge that anti-CTLA-4 or anti-CD40 better synergize with cancer vaccine when given at the time of the boost, rather than at the prime [166, 184]. Some combination of antibodies such as anti-PD-1 and anti-OX40 may be deleterious through the induction of apoptosis of T cells [185].

Lastly, for which patients, cancer vaccine may be indicated? For example, patients with natural immunity against targeted antigen should not be treated, as in the vast majority of studies, it appears that the amplification of preexisting immune response by cancer vaccine is quite rare likely due to tolerogenic or escape mechanism setup during host-tumor interaction [61, 67, 186–188]. High levels of myeloid-derived suppressive cells also correlated with resistance to immune response induced by cancer vaccine [189].

We hope that these few recommendations derived from lessons learned from past vaccine failures will guide the development of cancer vaccine to clinical success.

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