Review

Cancer vaccine: learning lessons from immune checkpoint inhibitors

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Abstract

Cancer vaccines have been exclusively studied all through the past decades, and have made exceptional achievements in cancer treatment. Few cancer vaccines have been approved by the US Food and Drug Administration (FDA), for instance, Provenge, which was approved for the treatment of prostate carcinoma in 2012. Moreover, more recently, T-VEC got approval for the treatment of melanoma. While, the overall therapeutic effects of cancer vaccines have been taken into consideration as below expectations, low antigenicity of targeting antigen and tumor heterogeneity are the two key limiting barriers encountered by the cancer vaccines. Nonetheless, recent developments in cancer immune-therapies together with associated technologies, for instance the unparalleled achievements bagged by immune checkpoint inhibitor based therapies and neo-antigen identification tools, envisage potential improvements in cancer vaccines in respect to the treatments of malignancies. This review brings forth measures for the purpose of refining therapeutic cancer vaccines by learning lessons from the success of PD-1 inhibitor based immune-therapies.

Key words: Cancer vaccine, immune checkpoint inhibitor, PD-1, combination therapy, immunotherapy

Introduction

Different from preventive vaccines, put to use on healthy individuals for the prevention of diseases, therapeutic cancer vaccines are directly used on cancer patients for the purpose of eliminating cancer cells through strengthening patients’ own immune responses, particularly CD8+ T cell mediated responses, with the assistance of suitable adjuvants [1-3]. Since pioneered by Dr. William Coley for the stimulation of patient’s immune system with the use of intratumoral injection of Coley’s Toxin (inactivated Streptococcus pyogenes and Serratia marcescens) in 1890s, the field of cancer vaccine has been quite active, introducing several kinds of cancer vaccines, for instance DC cell based vaccines [4, 5], peptide/protein vaccines [6, 7], genetic vaccines [8] and tumor cell vaccines [9], targeting various cancer cell antigens, including cancer testis antigens, differentiation antigens, oncofetal antigens, EMT (Epithelial-Mesenchymal Transition) factors and TME (Tumor Microenvironment) factors [10]. Determination of the therapeutic efficacy of cancer vaccines is made by taking into account many factors, include differential expression of targets between tumor cells and normal cells, the immunogenicity of vaccines and the antigenicity of targets within tumor microenvironment [7, 11, 12]. Thus, the paucity of TSAs (tumor specific antigens), immune suppressive effect of tumor microenvironment and tumor heterogeneity pose to be the key limiting barriers encountered by cancer vaccines [13-16].

By targeting immune suppressive microenvironment for the release of cytotoxic T cells, immune checkpoint inhibitors have attained unparalleled success as regards the treatment of cancers [17-19]. Ipilimumab, an anti-CTLA-4 antibody, received approval from the FDA for the
treatment of melanoma in 2011 [20, 21]. Nivolumab and pembrolizumab were approved in 2014 for the treatment of melanoma and squamous non-small cell lung cancer (NSCLC) [22-24]. The mechanistic research works brought to light the fact that the therapeutic efficacy of anti-PD-1/PD-L1 antibodies was associated with somatic mutation load of tumor tissue and subsequent neo-antigen number through the comparison of mis-match repair (MMR) proficient and MMR deficient patients [25-29]. The neo-antigens are now recognized as determinants for immune response of numerous immune-therapies [30-32]. The development in associated technologies, for instance neo-antigen predicting tools and antigenicity assessment tools, together with the decreasing cost of the next-generation sequencing, make scientist assessing tools, together with the decreasing cost of neo-antigen predicting tools and antigenicity development in associated technologies, for instance co-culturing with prostatic acid phosphatase (PAP) developed by loading DCs 

Thus, in this review, we primarily throw discussion on the barriers that are limiting the applications of cancer vaccines. Moreover, thereafter, it would proceed with exploring the neo-antigens and lessons from the success of immune checkpoint inhibitor based immune-therapies for refining the cancer vaccines.

Obstacles limiting cancer vaccines

As stated earlier, the therapeutic efficacy of cancer vaccine is dependent on the differential expression of target antigens by tumor cells as well as normal cells [11]. That is why TSAs are theoretically given preference to TAAAs in cancer vaccine design [14]. Since the first immunogenic antigen MAGE-1 was brought to light, several immunogenic antigens have been reported [36, 37]. But majority of them is shared TAAs that are expressed by both tumor cells and normal cells, despite the fact that, at a relative lower level, the on-target/off tumor effects pose to be potential threats [38, 39]. Furthermore, shared TAAs can be classified into three groups: 1) cancer-testis antigens; 2) tissue differentiation antigens; and 3) over-expressed antigens (table. 1) [40]. Conversely, TAAs are not taken into consideration as the optimal choices for cancer vaccine because of the two key reasons other than being shared by normal tissues: 1) low antigenicity, implying that TAAs are typically tolerated even as “self”, in this way, majority of vaccines targeting TAAs are put to application in means of combination with immunogenicity enhancers, like co-stimulatory cytokine granulocyte-macrophage colony stimulating factor (GM-CSF) together with TLR agonist, for instance, provegyn is developed by loading DCs in vitro through co-culturing with prostatic acid phosphatase (PAP) and GM-CSF fusion protein [41, 42]; 2) heterogeneity, heterogeneity among tumor cells within the same tissue is likely to lead to the selection of TAA negative tumor cells, heterogeneity among patients are likely to lead to personalized cancer vaccine requirement that is with constrained application in clinic because of elevated cost and intense labor in personalized epitope identification [43, 44].

| target type   | example  | limitations                                                                 | reference   |
|--------------|----------|-------------------------------------------------------------------------------|-------------|
| shared TAAs  | cancer-testis antigens | NY-ESO-1, MAGE-A1, SNS-2 | 1. Low antigenicity; 2. Activate limited type of T cell responses; 3. Non-driver mutation resources; 4. On-target side effect on normal tissues. | [1]         |
| differentiation antigens | Gp100, Mart-1, PSA | hTERT, surviving, MUC1 | 1. Low antigenicity; 2. Activate limited type of T cell responses; 3. Non-driver mutation resources; 4. Difficult to identify. | [27]        |
| over-expressed antigens | 1.2.3.4. | 1.2.3.4. | 1.2.3.4. | [45-48] |

TSAs: Neo-antigens  
EGFRVIII, ERBB2|PSH|, KRAS|ID|, BRAF|ID|,  
1. Low antigenicity; 2. Activate limited type of T cell responses; 3. Non-driver mutation resources; 4. Difficult to identify.  

In theory, the ideal antigens for cancer vaccines are clonal immunogenic TSAs that are specifically expressed and shared by all the tumor cells together with being efficient in eliciting immune responses from hosts [11]. Nonetheless, with the paucity of TSAs, numerous alternative approaches have been suggested whereby one is targeting multiple TAAs or even full-length protein in combination with immune response enhancers for the purpose of better eliciting both CD4+ and CD8+ T cell responses, for instance PANVAC targets CEA and MUC-1 antigens and encodes enhancing sequences for both targets [49]. Despite that fact, the cancer vaccine is still encountering the challenges of low-antigenicity and heterogeneity. Thus, novel strategies are in desperately required to enhance the efficiency of cancer vaccines.

Lessons learned from immune checkpoint inhibitors

The immune checkpoint inhibitors based immunotherapies have attained exceptional achievements in addition to refreshing the field of cancer treatment [50]. The underlying mechanisms of checkpoint inhibitors and cancer vaccines are to some level similar, harnessing patients’ own immune

Table 1. Classification of tumor antigens in cancer vaccine and related limitations

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system to fight against cancers [51, 52]. In this way, numerous lessons can be learned from immune checkpoint inhibitor based immunotherapy to cancer vaccines.

Tumors are considered to have evolved from thousands of somatic mutations that develop tumor cells’ growth as well as survival benefits over normal cells [53, 54]. All through the development of tumors, tumor cells adopt numerous mechanisms for the purpose of escaping from the surveillance of host immune system, a major one is developing immune suppressive microenvironment in order to suppress the function of immune effectors, for instance CD8+ T cells, through expressing immune checkpoints, like CTLA-4, LAG-3, Tim-3 and PD-1 [55]. Through the discovery of this mechanism, there have been developed numerous for the purpose of targeting those immune checkpoints, such as PD-1 inhibitors, Nivolumab and Pembrolizumab that have been both appraised and approved by the FDA in respect of the treatment of melanoma, non-small cell lung cancer (NSCLC) and melanoma respectively [50]. Furthermore, the therapeutic efficiency of PD-1 inhibitors was reported having association with the somatic mutation load, which is coupled with the dysfunction of MMR system [38]. It implies that the higher somatic mutation load of the patients together with the higher number of neo-antigens will be encoded, and the higher response rate of the patients will be attained from PD-1 inhibitors [56]. In this way, the diversity of neo-antigens within the tumor tissues of patients poses to be a key determinant for immunotherapy response.

**Targeting Immunogenic Neo-antigens**

It has been revealed by several research works that, among neo-antigens, many are immunogenic, effective in eliciting immune response from host in vitro and in vivo [57, 58]. That is why identification of immunogenic neo-antigens possesses critical importance for the application of neo-antigens to cancer vaccines. With the development of associated technologies, for instance Next-generation Sequencing (NGS), peptide manufacturing and peptide immunogenicity in silico prediction, targeting tumor specific neo-antigen is now turning out to be a sound reality [33]. For the purpose of overcoming the low antigenicity issue, cancer vaccines can be designed in order to target immunogenic neo-antigens. For the purpose of tackling the heterogeneity issue, numerous immunogenic neo-antigens are advised to target in the meantime, in case of the selection of targeting neo-antigen negative tumor cells [56]. Among these somatic mutations that encode immunogenic neo-antigens, there are some considered to be driver mutations that are defined essential for the development of tumors [59]. This is how cancer vaccines can be further designed to target immunogenic neo-antigens that are derived from driver mutations. This point was affirmed by a recent research work, throwing light on the fact that the heterogeneity of neo-antigens within a single tumor tissue determines the immuno-reactivity as well as sensitivity to immune checkpoint inhibitors [60]. All through the development of tumors, the number of driver mutations boosts up. In this way, the early staged NSCLC patients possess higher number of clonal neo-antigens, clonally encoded and shared by tumor cells, together with the lower neo-antigen heterogeneity, associated with improved clinical performance of immune checkpoint inhibitor based immunotherapies [61]. Some scientists even proposed cancer immuno-prevention by cancer vaccines to individuals without cancers, but at high risk of having cancers [62].

Together with targeting multiple immunogenic neo-antigens or immunogenic clonal neo-antigens, it determines the efficiency of immune checkpoint inhibitors based immune-therapies. Another lesson can be learned, among cancers, melanoma is taken into account to be the most somatic mutation loaded cancer [59]. Furthermore, speculation can be drawn from this that melanoma patients possess the biggest number of neo-antigens, and perhaps the clonal neo-antigens, derived from driver mutations, some of which are shared by different types of cancers [63]. Consequently, the whole tumor cell derived from patients, containing shared clonal neo-antigens can be put to application as autologous cancer vaccines or even allogeneic cancer vaccines catering to HLA matching scenario. In the same fashion, autologous cancer vaccines or even allogeneic cancer vaccines can be made out of tumor tissues from the majority of responsive patients for the purpose of treating the same cancers or even different types of cancers under HLA matching scenario.

To conclude, there are at least three lessons that can be learned from immune checkpoint inhibitor based immunotherapies to cancer vaccines for the purpose of overcoming the low antigenicity and heterogeneity issues by targeting neo-antigens: 1) targeting multiple immunogenic neo-antigens; 2) targeting immunogenic clonal neo-antigens; 3) deriving tumor cell based cancer vaccines from the most immunogenic clonal neo-antigens loaded patients.

**Combine with immune checkpoint inhibitors**

Cancer vaccines are designed to bring forth the immunogenic antigens to excite patients’ own
immune system, particular tumor specific CD8+ T cell responses [1]. Immune checkpoint inhibitors are designed for the release of the patients’ own effects or cells from suppressed state. Majority of patients is not responsive to immune checkpoint inhibitors because of the lack of tumor specific effector cells [64-66]. While, cancer vaccine has been revealed with the ability to elicit diverse neo-antigen specific effector cells [67, 68]. This is how it is quite adequate to apply cancer vaccines providing tumor specific T cells before immune checkpoint inhibitor based immunotherapies [67, 69]. It has been brought to light by the studies that this combination showcases more effectiveness in comparison with either mono-therapy by promotion of cytotoxic T cell activity, facilitation of effector T cell infiltration and accumulation of memory precursor CD8+ T Cells [70-72]. Therefore, cancer vaccines are considered to be perfectly matching immune checkpoint inhibitors [73]. Moreover, there are several ongoing clinical trials (table 2).

For the purpose of further delivering diversely enough CD8+ T cells with cancer vaccines, numerous approaches can be followed in order to improve the efficiency of the combination of cancer vaccines and immune checkpoint inhibitors. It has been well documented that IFN-γ is capable of inducing the expression of MHC molecules from tumor cells [74, 75]. On these bases of this notion, in whole tumor cells design, for the purpose of better providing stimulations from diversely enough antigens, tumor cells can be cultured with suitable amount of IFN-γ possessing medium or genetically manipulated to express IFN-γ prior to the application in combination with immune checkpoint inhibitors. Moreover, the expression of PD-L1 on tumor cells that can be further induced by IFN-γ, is likely to stand for another factor that adversely influences the efficiency of tumor cell vaccines [76]. In this way it is interesting to carry out the investigation of the influence of knock-down or knock-out the expression of PD-L1 of tumor cell vaccines on the combination of cancer vaccines with immune checkpoint inhibitors.

Table 2. Part of clinical trials investigating combination of cancer vaccine with checkpoint inhibitors

| Agent                     | Malignance                          | Phase | Status/results | NCT Identifier |
|---------------------------|-------------------------------------|-------|----------------|----------------|
| GVAX+Nivolumab            | Pancreatic cancer                    | I/II  | Recruiting     | NCT02431982    |
| DC AML                    | Acute myelogenous leukemia           | II    | Recruiting     | NCT01996602    |
| Vaccine+CT-011            | Hormone-Resistant, Metastatic        | I/II  | Recruiting     | NCT02499835    |
| pTVG-HP Plasmid DNA Vaccine+ | Prostate Cancer                   |       |                |                |
| pembrolizumab             | DC Vaccines+                         |       | Recruiting     | NCT02529072    |
| nivolumab                 | Provenge + CT-011                    | II    | Recruiting     | NCT01420965    |
| or Without                | GAVX+CRS207 With or Without Nivolumab| II    | Recruiting     | NCT02443371    |
| TPLDC Vaccine + checkpoint inhibitors | Metastatic Adenocarcinoma of the Pancreas | I/II | Recruiting     | NCT02678741    |
| pembrolizumab             | Melanoma                             | I     | Recruiting     | NCT02574533    |
| Vigil™ vaccine+           | Melanoma                             | I     | Recruiting     | NCT02385669    |
| pembrolizumab             | Melanoma                             | I     | Recruiting     | NCT02385669    |

GVAX: Granulocyte-macrophage Colony-stimulating Factor (GM-CSF)  
Gene-transfected Tumor Cell Vaccine; DC: Dendritic Cell; AML: Acute Myelocytic Leukemia; CT-011: Pidilizumab, Pembrolizumab and Nivolumab, programmed cell death 1 blockade inhibitors; pTVG-HP: DNA vaccine encoding Prostate acid phosphatase (PAP); CRS-207: live-attenuated Listeria vaccine expressing mesothelin; TPLDC: tumor lysate particle-loaded dendritic cell vaccine; Vigil™: GMCSF/bisDNA furin DNA engineered autologous tumor cell product; 6MHP: six melanoma-associated helper peptides vaccine; ipilimumab: cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) antibody.

Hence, in addition to targeting neo-antigens, there are still numerous lessons that can be learned from immune checkpoint inhibitor based immuno-therapies to cancer vaccines by combining with immune checkpoint inhibitors; 1) culturing tumor cells with IFN-γ containing medium prior to application as cancer vaccines in combination with immune checkpoint inhibitors; 2) genetically manipulating tumor cells to secrete IFN-γ prior to application as cancer vaccines in combination with immune checkpoint inhibitors; 3) ablating the expression of PD-L1 on tumor cells prior to application as cancer vaccines in combination with immune checkpoint inhibitors (table 3).

Table 3. Lessons can be learned from immune checkpoint inhibitors to cancer vaccines

| Cancer Vaccine | Major Challenges | Strategies |
|----------------|------------------|------------|
|                | Low antigenicity | Targeting neo-antigens: |
|                |                  | 1. targeting multiple immunogenic neo-antigens; |
|                |                  | 2. targeting clonal neo-antigens; |
|                |                  | 3. develop cancer vaccines from immune checkpoint inhibitor responsive tumor tissues. |
|                | Heterogeneity    | Combine with immune checkpoint inhibitors: |
|                |                  | 4. culturing tumor cells with IFN-γ containing medium ahead; |
|                |                  | 5. genetically manipulate tumor cells to secret IFN-γ ahead; |
|                |                  | 6. delete the expressing of PD-L1 on tumor cell vaccine. |
Conclusion
With the development of associated technologies, lessons can be learned to target neo-antigens of cancer vaccines from immune checkpoint inhibitors, and those neo-antigens should better be clonal and immunogenic. For the purpose of better provoking the patients’ own immune responses, cancer vaccines together with immune checkpoint inhibitor can be perfectly combined with each other. Furthermore, additional modifications, such as knocking down the expression of PD-L1 or addition of IFN-γ secretion to tumor cell-based vaccines, can also be incorporated to better equip this combination (Fig. 1). Moreover, it goes without saying that the type of cancer vaccines, the reliability of neo-antigen identification tools, vector type, ratio dosage of cancer vaccines and immune checkpoint inhibitors and other factors are also required to be reckoned with.

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Competing Interests
The authors have declared that no competing interest exists.

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8: 1-3.
7: 254-63.
6: 425-40.
5: 111-3.
4: 95-100.
3: 3401-12.
2: 287-302.
1: 425-32.
1: 157-164.
1: 14949-50.
1: 501-13.
1081-91.
287-302.
143-53.
13: 143-58.
12: 753-740.
11: 287-302.
10: 3400-5.
9: 1094-103.
8: 41641-69.
7: 166-172.
6: 1422-30.
5: 108-11.
4: 2-3.
3: 341-21.
2: 353-63.
1: 207-12.
10: 329-305.
7: 425-40.
6: 5171-22.
5: 267-302.
4: 1643-7.
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