Review Article: Internal Medicine: Immunology

Research advance in tumor specific antigens

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Abstract: Whether or not there are "tumor antigens" recognized by T cells had been controversial, until mouse and human tumor antigens have been identified one after another since the 1980s. In recent years, advances in genome sequencing technology have made possible to identify neo-antigens based on patient-specific gene mutations. Successful findings of immune checkpoint inhibitors (ICIs) in clinical trials have shed a light on tumor antigens which plays a key role so that they could be a candidate of novel therapeutic target. Since correlation between response to ICIs and neo-antigen has been clarified, it has become gradually clear that the immune response recognizing the neo-antigens plays a central role in anti-cancer immunity. Neo-antigens can elicit a strong immune response and are promising targets for novel cancer vaccine therapy or T-cell therapy, even though there are still some issues such as exhaustion and refractory state of T cells that they recognize. There are some types of tumor antigens with various specificity and immunogenicity to subject tumor. Several approaches utilizing tumor specific antigens are emerging as candidates of combination therapy together with ICI to maximize benefit from ICI treatment. Further studies of cancer antigens are expected to be the key to the next breakthrough in immunotherapy.

Keywords: Immunotherapy; tumor antigens; neo-antigens; immune checkpoint inhibitors (ICIs); vaccine

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Introduction

Cancer immunotherapy is emerging as a newly developed standard treatment strategy in some types of cancers. Since immune checkpoint inhibitors (ICIs) have achieved improvement of survival outcomes comparing with standard cytotoxic chemotherapy in some settings of various malignancies, it has been recognized as one of the standard therapeutic options. On the other hand, it is further clinical need to identify biomarkers in predicting response to ICIs as well as agents facilitating its efficacy. Tumor specific antigens recognized by T cells are emerging, as they reportedly play a key role in anti-tumor immune response. Many researchers had attempted to identify high immunogenic tumor specific antigens which could be a novel target of T cell therapy and cancer vaccination therapy. Thus, most current efforts in cancer immunotherapy are focusing on induction of tumor-specific T cell response with tumor specific antigens. In the current article, we are comprehensively reviewing overview and future perspective of tumor specific antigens in cancer immunotherapy with key publications.

History of identifying cancer antigens

First attempt of immunotherapy has been documented

since 1890s, to facilitate anti-tumor immunity with using bacterial extracts. William B. Coley, a surgeon in New York Hospital reported that he administered heat-killed Streptococcus pyogenes and Serratia marcescens to patients with inoperable soft tissue sarcoma and over 50% of cases achieved complete tumor regression at the time of therapy, exhibiting subsequently more than 5-year survival (1). He also found that the treatment efficacy is positively correlated with height of fever (2). Thus, it is generally recognized that the efficacy of Coley's toxin attributed to the anti-cancer immune response. Although the response rates that they reported unsurpassed by modern immunotherapy, subsequent researchers did not demonstrate similar efficacy, especially in carcinoma patients who had been treated with Coley's toxin (3). The reason why Coley's toxin failed in carcinoma patients may be that the mechanism of its efficacy depends on non-specific immune activation.

There had been long controversy whether tumor cells originated from host own normal cells could be recognized by host immune cells. In 1953, Foley reported that implantation of methylcholanthrene-induced sarcoma lead immunity against same sarcomas, resulting in preventing its growth (4). As "immune tolerance" had been elucidated (5,6), it became to be considered skeptical in general.

After 1970s, several researchers demonstrated that chemical carcinogenesis exhibited various cancer antigens for each mouse which could not induce immunity by transplantation into other mouse even with same genetic background as well as same chemical carcinogenesis method (7,8). Since Ikeda *et al.* reported that methylcholanthrene-induced sarcomas elicited significantly stronger cytotoxic T cell response and stable compared with non-chemical-induced ones (9). Their findings may suggest difficulty of applying cancer antigen-based immunotherapy in clinical practice. Thereafter, since 1980s, "cancer antigens" recognized by host T cells in mice model was based on individual acquired genetic alterations, which was so-called "neo-antigens" (9,10). In addition, cancer-testis antigens MAGE (human) and P1A (mouse) were identified as "cancer antigens" (11,12). They are expressed in a variety of cancers, but not in normal adult tissues except for the testis. Therefore, cancer-testis antigen became emerging target for immunotherapy (13,14). Then, methodology for identifying cancer antigens have been gradually advanced, especially gene sequencing technique has been rapidly progressed. In 2005, Lennerz *et al.* identified five neo-antigens derived from somatic mutations in addition to three previously unknown peptides processed from melanosomal proteins tyrosinase and demonstrated a dominant role of neoantigen-specific T cells in controlling melanoma (15). After that, neo-antigens have become the next target for immunotherapy as next-generation sequencing has been commercially applied for research as well as clinical practice (16).

Classes of tumor antigens recognized by T cells

"Tumor antigens" recognized by T cells are not necessarily expressed in a tumor-specific manner. They include antigens expressed in cancer cells as well as some part of normal cells in some extent, those overexpressed in cancer cells, and those exclusively expressed in cancer cells but not in normal cells as shown in *Figure 1* (17).

Tissue differentiation antigens

Differentiation antigens are specifically expressed in tumor cells and normal cells of tissue which is origin of the tumor with the specific feature of tissue differentiation. The first literature regarding this type of antigens by Anichini *et al.* demonstrated that cytotoxic T cells in melanoma patients can recognize both tumor cells and normal melanocytes through "tumor antigens" (18). In melanoma patients, tissue differentiation antigen expression was shared between tumor cells and melanocytes, gp100, Melan A/MART-1, tyrosinase, and so on (19). They were enzymes which are specifically expressed in melanosomes in normal melanocytes and overexpress in melanoma cells so that the difference of expression levels could be distinguishable (20).

As a target for immunotherapy, vaccination therapy with melanocyte differentiation antigens including Melan-A/MART-1, tyrosinase, and gp100 demonstrated objective response rate of 2.5% in patients with metastatic melanoma in integrated analysis of the clinical trials (21). In addition, ocular and systemic autoimmunity-related adverse events in melanocyte differentiation antigens treatment were also reported (22,23). Thus, tissue differentiation antigens have gradually become out of focus as a target of immunotherapy.

Overexpressed antigens

Antitumor immune response should begin recognition of tumor antigens in which a minimal number of HLA-peptide complexes that displayed at the cell surface were required. The threshold should contribute to tumor specificity for T cells recognizing peptides derived from proteins that are overexpressed in tumor cells comparing to normal cells. This

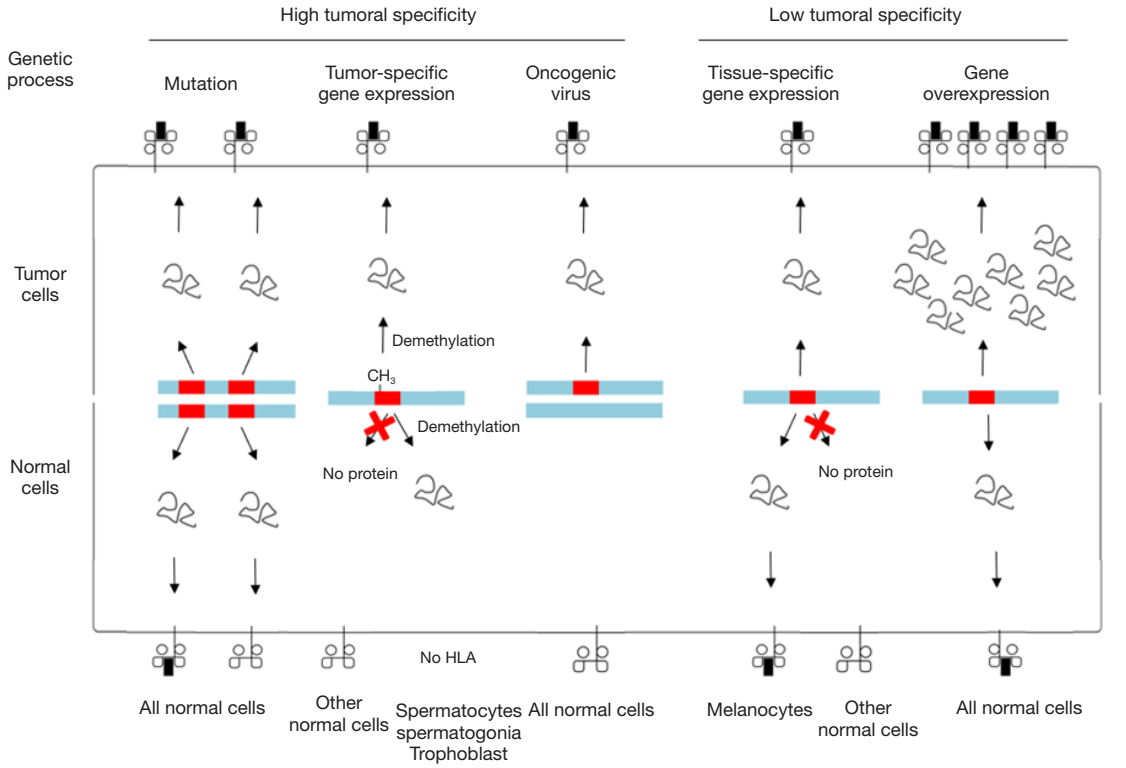

Figure 1 Major classes of tumor antigens recognized by CD8 T cells on tumors.

type of tumor antigens is called as "overexpressed antigens" highly expressed in cancer cells, which mainly play a relevant role in the growth and survival of cancer cells. For example, WT-1, Her-2/neu, and CEA are overexpressed in various types of cancer. For clinical application, it is considerable issue that the antigenicity and specificity of overexpressed antigens are not sufficient. A large difference in expression levels between normal and tumor tissues is necessary to be specifically recognized by T cells.

The oncogene encoding the growth factor receptor, Her-2/neu, is overexpressed in many epithelial malignancies including ovarian and breast cancer. A number of clinical trials investigating overexpressed antigens have demonstrated limited efficacy and some adverse effects (21,24-26).

Cancer-testis antigens

Cancer-testis antigens exclusively express in normal testis, normal placenta, and cancer tissue, sharing among patients with each type of cancer. Since gonadal tissue does not express HLA class I that means not to be recognized as a target of cytotoxic T cells, it is considered that this type of antigens can lead immune response in tumor-specific manner. The first cancer-testis antigen, MAGEA1 was discovered in the 1990s (12,27). Various cancer-testis antigens including MAGE, NY-ESO-1 and XAGE1 have been identified (28) and they reportedly have high tumor antigenicity that could be applied for promising immunotherapeutic target (29).

Cancer-testis antigens including MAGE and NY-ESO-1 have been investigated in clinical trials, demonstrating limited efficacy as cancer vaccine treatment (21,30,31). It should be noted that some of cancer-testis antigens are expressed normal tissues in the embryonic period, some adult tissues, and in addition highly homologous family molecules are expressed in normal tissue, even though most of them have high antigenicity that may be expected to be good targets for cancer immunotherapy.

Viral antigens

Some viruses are involved in carcinogenesis, and they are said to contribute to the development of cancer in about 20% (32), and gene products derived from viruses may act as tumor antigen peptides. Human T-cell leukemia virus,

Table 1 Classes of tumor antigens and the characteristics

Characteristics	Classes of tumor antigens				
	Differentiation antigens	Overexpressed antigens	Cancer-testis antigens	Viral antigens	Neo-antigens
Antigenicity	+/– or +	+/– or +	+/++	++	++
T cell affinity	+/– or +	+/– or +	+/++	++	++
Immune tolerance	+/–	+/–	– or +/–	–	–

Epstein-Barr virus associated with head and neck cancer, high-risk human papillomavirus (HPV) is recognized by the immune system as a cancer rejection antigen associated with oncogenesis. Among them, HPV virus antigens E6 and E7 showed high expression in cervical cancer which can be target antigens for cytotoxic T cells. However, there are a limited number of clinical trials investigating the efficacy and feasibility of viral antigen vaccine therapy to date (33,34).

Neo-antigens

In multi-step process of carcinogenesis, important gene mutations related to cell proliferation, growth and survival (i.e., driver gene mutations), abundant of concomitant mutations caused by genomic instability related to cancer-inducing factors including ultraviolet rays and tobacco smoking (i.e., passenger mutations) accumulate in somatic genes. Proteins derived from cancer-specific gene mutations are non-self proteins that do not exist in normal tissues and mostly unique to each patient are called neo-antigens. T cells do not acquire immune tolerance to neo-antigens during the differentiation process in the thymus, and thus can induce a strong immune response to the neo-antigens. On the other hand, since this reaction does not occur in normal cells and is tumor-specific, neo-antigens are considered as ideal therapeutic targets of cancer immunotherapy in various malignancies.

Biomarkers utilizing tumor antigens

While tumor specific antigens could be candidates of therapeutic targets, it could also be utilized for tumor detection and diagnosis. Tumor antigens are frequently detected in peripheral blood as they are often released into tumor blood vessels. Further, tumor antigens which usually present within intracellular matrix or organelles are much greater released when chemotherapy or radiotherapy cause tumor cell death. Thus, they could be useful also in evaluating therapeutic response and risk of relapse after treatment. Recent advances in technologies enable to easily obtain protein-based biomarkers including tumor antigens. For example, prostate specific antigen (PSA), which is classified as tissue differentiation antigens, are widely used as a diagnostic and predictive marker in prostate cancer (35). There are considerable numbers of tumor antigens other than PSA, which can be utilized as diagnostic markers, including survivin in breast cancer (36), MAGE in hepatocellular carcinoma (37), and NY-ESO-1 and TP53 in ovarian cancer (38). However, these markers other than PSA are not routinely used and not commercially available in general practice as the specificity and sensitivity are limited.

Summary of conventional vaccine therapy

Cancer vaccine therapy is a treatment method that induces a tumor-specific immune response in patient body by directly administering cancer antigens into the patient in a variety of forms to suppress the progression of cancer or eliminate the cancer. Conventionally, cancer vaccine had been developed focusing on shared-antigens that are commonly expressed, but few have been shown to be effective (21). Since shared-antigens such as tissue differentiation antigens, overexpressed antigens, and cancer-testis antigens have been used as targets of cancer vaccine, T cell receptor (TCR) of specific T cells have almost low to intermediate affinity after negative selection of high affinity TCRs in the thymus (*Table 1*). That may be why conventional cancer vaccine therapy did not show sufficient efficacy in clinical trials to date. It was reported that even cancer-testis antigens which are considered to have high antigenicity, to rarely have high affinity TCRs in human (39). Also, it is also possible that the T cells were exposed to cancer antigens even before vaccination, resulting in fatigue and refractory conditions. Cytotoxic T cells against MART-1 antigen derived from

self-antigens have been reported to be refractory to antigen stimulation by regulatory T cell-mediated induction of anergy (40). Altogether, clinical trials have suggested that it may be required other approach overcoming the immune-regulatory mechanisms above.

ICIs and tumor antigens

ICIs targeting molecules such as PD-1/PD-L1 in the immune checkpoint mechanism that suppresses immune hyper-response have been shown to have effectiveness in clinical trials (41-43). On those successful results, ICIs have become one of the standard therapeutic options. Since the objective response rate is not so high, on the other hand, identification of biomarkers for predicting the response for ICIs is emerging issue.

Advances in next-generation sequencing and bioinformatics technologies can provide identification of individual gene mutations in whole genome on patient-basis. On this background, neo-antigens derived from individual gene mutations has become reemerging as a target for immunotherapy. It was reported that the number of gene mutations and the number of predicted neoantigens was significantly correlated with the response rate in non-small cell lung cancer and melanoma where the number of gene mutations and the number of predicted neoantigens were relatively high (44). In addition, cancers with mutated mismatch repair genes exhibited to significantly correlate to response to anti-PD-1 antibodies treatment (45). Then, the mechanism is reported to be associated with microsatellite instability and the number of gene mutations (46). Whereas, in a clinical trial of anti-PD-1 antibody in patients with advanced Merkel cell carcinoma, there was no significant difference in response rate between positive and negative cases of Merkel cell polyomavirus (MCPyV) which is associated with carcinogenesis (47). Merkel cell carcinoma cases demonstrated comparable response rate regardless of positive or negative for MCPyV which is positively correlated with burden of somatic gene mutations, indicating that not only neo-antigens but also T cells that recognize viral antigens involved in the efficacy of ICIs (48). Moreover, Anagnostou *et al.* documented that a total of 41 neoantigens (7–18 per case) disappeared when four cases showed progressive disease after response to ICI treatment among patients with NSCLC (49). It was suggested that tumor regression by ICIs is mediated by an immune response to neo-antigens, and that the disappearance of neo-antigens may be one of the mechanisms of acquired resistance. Also, loss of antigen presentation caused by genetic alterations involved antigen presentations such as B2M (50) and HLA (51) have been reported.

Since recent breakthrough by ICI have changed clinical practice of various types of cancer worldwide. Especially, treatment strategy of NSCLC has drastically changed by ICI (41-43). The change has great impact on public health as NSCLC is the major cause of cancer-related death. On the background, it is clinically and socially significant in this area.

In particular, recent clinical trials revealed an emerging issue that response rate to ICI ranged only 15–25% in NSCLC patients and most had primary resistance (41-43). It is thus required to overcome the resistance and shed light on approaches to combine several treatment choices with ICI to maximize the therapeutic benefit from ICI. It is required to broaden the application of immunotherapy including ICI to identify novel therapeutic targets and/or to develop new therapeutic agents modulating immune response. Proposed approaches which possibly induce immunogenicity of cancer cells includes immunogenic cell death (52) led by chemotherapy (53), irradiation (54,55), or chemoradiotherapy (56). This mechanism also facilitates lymphocyte migration to tumor sites, thereby sensitizing tumors to ICI therapy.

To overcome the resistance caused by a loss of antigen presentations may require strategies that eliminate cancers independent of HLA, such as adoptive cell therapy with NK cells or chimeric antigen receptor T cells (57). Recent progress of the adoptive cell therapeutic options may bring benefit hematological and solid malignancies including lung cancer in the near future (58).

Immunotherapy targeting neo-antigens

Since it has been clarified that immune response to neo-antigens play a key role in anti-cancer immunity, cancer vaccine therapy and T cell infusion therapy targeting neo-antigens has been emerging. Although gradual improvement of next-generation sequencing may contribute to individualized immunotherapy based on somatic gene mutations of each patient, immune response to candidate neo-antigens should be verify using tumor infiltrating lymphocytes and peripheral blood lymphocytes in actual.

Anti-tumor effect and suppression of metastasis in addition to feasibility are demonstrated in clinical trial of peptide vaccine treatment targeting neo-antigens in melanoma (59) and glioblastoma (60). The successful

results may be caused by that targeting multiple antigens against heterogeneous prevent tumor immune escape. In addition, when an ICI was administered to a case where tumor re-growth occurred during the treatment course of cancer vaccine, disease control was again achieved and the reactivity of specific T cells to the antigens used as the vaccine target was enhanced again (60).

Although neo-antigen has several advantages compared to other tumor antigens, there are some issues including immuno-editing which suppress anti-tumor immune response and exhaustion due to long-term exposure of T cells to the antigens. It can be overcome by combining with immunotherapy having different action points and selecting multiple epitopes. Although cost of sequencing has dropped dramatically, the cost of developing an individualized vaccine is enormous for now.

Summary

Immunotherapy has become emerging again as ICI achieved successful results in clinical trials. Clinical significance of neo-antigens was widely recognized due to association with its relation to response to ICI treatment. Neo-antigens can induce high affinity T cells and has a great advantage that it is not expressed in normal cells at all. On the other hand, there are still some issues to be overcome including exhaustion of T-cells and mechanism of immune editing. Neo-antigens have superiority as therapeutic targets and further research on anti-tumor antigens is expected to be the key to the next breakthrough in immunotherapy.

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