Tumor Immunology –Principles and Translations–

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Recently, immune checkpoint blockade with anti-CTLA-4 and anti-PD-1 antibodies has the greatest impact on clinical cancer therapy. The rationale for these therapeutic regimens has been established by our advanced knowledge about basic immunology, such as the identification of tumor antigens and the elucidation of self-tolerance mechanisms, and proof-of-concept experiments in animal models. More applications of the immunostimulatory antibodies targeting costimulatory molecules, such as CD40 and CD137, and coinhibitory molecules, such as TIM-3 and VISTA, are now expected. Accumulating evidence shows that these immunostimulatory antibodies can be successfully combined with conventional chemotherapy and radiotherapy to improve their efficacy.

Key words: cancer immunotherapy, checkpoint blockade, CTLA-4, PD-1

Introduction

Cancer immunotherapy using monoclonal antibodies (mAbs) targeting tumor cells, such as rituximab against non-Hodgkin's lymphoma and trastuzumab against breast cancer, has been established as the standard therapy. These therapeutic mAbs exert antitumor effects mainly by recruiting host effector cells, such as NK cells and macrophages mediating antibody-dependent cellular cytotoxicity (ADCC), and host effector molecules, such as complements mediating complement-dependent cytotoxicity (CDC). Recently, a paradigm shift has been made in the antibody therapy by the approval of anti-CTLA-4 mAb (ipilimumab)¹⁾ by FDA against advanced melanoma in 2011. This mAb does not target tumor cells directly, but blocks the coinhibitory CTLA-4 (cytotoxic T-lymphocyte antigen-4) molecule expressed on T cells mediating feedback downregulation of T cell responses. Moreover, more promising results were obtained in clinical trials with a blocking mAb (nivolumab) against a similar coinhibitory molecule PD-1 (programmed death-1) in 2012²⁾. Based on

these great advances, a review titled "Cancer immunotherapy comes of age" was reported in the last issue of *Nature* in 2011³⁾. Then, the most remarkable topics in the 2013 ASCO meeting was a synergistic effect of the combination of nivolumab and ipilimumab in advanced melanoma patients, which has been published in *NEJM*⁴⁾. In the last issue of *Science* in 2013, Cancer Immunotherapy was selected as the Breakthrough of the Year⁵⁾. These therapeutic regimens using anti-CTLA-4 and anti-PD-1 mAbs to augment host antitumor immunity have been established by our advanced knowledge about peripheral tolerance mechanisms limiting autoimmunity as described below.

Basic principles of tumor immunology

The concept of tumor immunosurveillance, originally proposed by Burnet in 1957, has been substantiated by higher incidence of tumor development in immunodeficient mice and humans and identification of tumor antigens recognized by cytotoxic T lymphocytes (CTLs) specific for autologous tumor cells (Table-1). Except for oncogenic

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[Received May 30, 2014]

Table-1 Tumor antigens recognized by CTL

Oncogenic viral proteins: HPV16-E7 (cervical ca), HTLV-1 Tax (ATL)
Tumor-specific mutation : β -catenin (melanoma), CDK4 (melanoma), caspase-8 (squamous cell ca)
Tumor-specific over-expression: Her2 (mammary ca), survivin (stomach ca), CEA (colon ca), WT-1 (leukemia)
Cancer-testis antigens : NY-ESO-1 (melanoma), MAGE-1,2,3 (melanoma)
Tissue-specific differentiation antigens : gp100, MART-1/Melan-A, TRP2, tyrosinase (melanoma) PSA, PSMA (prostate ca)

HPV, human papillomavirus; HTLV, human T-lymphotropic virus; CEA, carcinoembryonic antigen; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen

viral proteins and point mutations in oncogenes or tumor suppressor genes, most of the tumor antigens are non-mutated self proteins, against which immune responses are limited by the self tolerance mechanisms (Table-2). In addition to the central tolerance mechanism by which self-reactive T cell clones are deleted in the thymus (negative selection), potentially autoreactive T cells recognizing peripheral tissue antigens, including tumor antigens, are anergized due to self antigen presentation by non-professional antigen-presenting cells (APCs) lacking costimulatory molecules such as B7. Moreover, an excess T cell response against persistent antigens, such as tumor antigens, are suppressed by coinhibitory molecules expressed on activated T cells, such as CTLA-4 and PD-1, establishing the immune checkpoints to avoid immunopathology. The important roles for CTLA-4 and PD-1 have been substantiated by the development of fatal autoimmune diseases in CTLA-4- or PD-1-deficient mice. Antitumor effects of blocking mAbs against CTLA-4 and PD-1 have been demonstrated against various tumor models in mice, which were mediated by enhancement of tumor-specific CTL responses. These findings led to the clinical translation of the checkpoint blockade to human cancer therapy.

Translations to cancer immunotherapy

In addition to the conventional antibody therapy targeting tumor cells via ADCC and CDC, agonistic

Table-2 Mechanisms of T-cell self tolerance

Central : Deletion of self-reactive clones in the thymus (Negative selection)
Peripheral :
1. Clonal anergy due to lack of co-stimulatory signal such as B7
2. Suppression by co-inhibitory signals such as CTLA-4 and PD-1
3. Suppression by regulatory T cells
4. Suppression by immuno-suppressive cytokines such as TGF- β

mAbs (such as lexatumumab) against DR5 (death receptor-5), which is a death-inducing receptor for TRAIL (tumor necrosis factor-related apoptosis-inducing ligand) and induces apoptosis preferentially in tumor cells, are now in phase II clinical trials against various cancers⁶⁾. We previously found in mouse models that initial regression of TRAIL-sensitive tumors by administration of anti-DR5 mAb (MD5-1) induced tumor-specific CTLs by recruitment of host APCs via Fc portion, which could also eradicate TRAIL-resistant mutants via perforin- and FasL-mediated cytotoxicity (Figure-1)⁷⁾. We then demonstrated that anti-tumor effects of anti-DR5 mAb could be synergistically enhanced by combination with immunostimulatory mAbs, such as agonistic mAb against CD40 activating APCs and agonistic mAb against CD137 (4-1BB) enhancing CTL activation⁸⁾. In addition, agonistic mAbs against other costimulatory molecules, such as CD134 (OX40) and CD27, also exerted antitumor effects in mouse models. Based on these findings, agonistic mAbs against human CD40, CD137, CD27, and CD134 are now under clinical trials or development. We and others have also demonstrated that blocking mAbs against coinhibitory molecules, such as CTLA-4, PD-1, TIM-3 (T cell immunoglobulin and mucin domain-containing molecule-3), VISTA (V-domain immunoglobulin-containing suppressor of T-cell activation), and B7-H3 exerted antitumor effects in various mouse tumor models as a single agent or in combination with chemotherapy⁹⁾⁻¹¹⁾. It has recently been shown that conventional chemotherapy and radiotherapy induce immunogenic cell death¹²⁾, which can result in induction of tumor-specific CTLs as did anti-DR5 mAb in Figure-1, and their

Figure-1 Enhancement of anti-DR5-mediated CTL induction by immunostimulatory Abs

Initial regression of TRAIL-sensitive tumors by administration of anti-DR5 mAb (MD5-1) induces tumor-specific CTLs by recruitment of host APCs via Fc portion, which can also eradicate TRAIL-resistant mutants via perforin- and FasL-mediated cytotoxicity. Such a CTL-mediated antitumor effect can be synergistically enhanced by combination with immunostimulatory mAbs, such as agonistic mAb against CD40 activating APCs and agonistic mAb against 4-1BB enhancing CTL activation, and checkpoint blockade with anti-CTLA-4 and anti-PD-1 mAbs.

efficacy can be greatly improved by combination with immunostimulatory mAbs, such as agonistic mAb against CD137 and blocking mAb against PD-1^{13) 14)}. These findings are immediately relevant to future clinical translations.

Perspective

So far, objective response was achieved in 40% of the melanoma patients treated with the combination of anti-PD-1 and anti-CTLA-4 mAbs, but 60% remained unresponsive⁴⁾. In addition, some tumor types such as prostate cancer and colorectal cancer were totally unresponsive to the anti-PD-1 therapy²⁾. Further basic studies using clinically relevant animal models are still needed to improve

the immunostimulatory antibody therapy against various cancers.

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