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Review article

Immunotherapy for advanced melanoma: Current knowledge and future directions

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ABSTRACT

Melanoma is one of the most aggressive cancers and is responsible for a large proportion of skin cancer-related deaths. The recent development of novel immunotherapeutic approaches has led to great advances in melanoma therapy. Because melanoma cells often express tumor-specific neo-antigens, significant therapeutic effects are mediated via immunotherapy-induced activation of cytotoxic T lymphocytes (CTLs); however, the effects depend on the immune status of the patient. At present, various immunotherapies have been approved and new clinical trials are progressing. These immunotherapies act in several ways, including CTL brake release, induction of CTL activation, transfer of CTLs, and modification of the tumor microenvironment to facilitate CTL activation. In the near future, patient-tailored immunotherapies and combination therapies are expected. In addition, it is important to monitor the status of the patient's immune response when selecting the most effective immunotherapy strategy.

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Abbreviations: APC, antigen-presenting cell; ATP, adenosine triphosphate; BRCA2, breast cancer susceptibility gene 2; CR, complete response; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; CSF1R, colony-stimulating factor 1 receptor; CTL, cytotoxic T lymphocyte; DC, dendritic cell; GITR, glucocorticoid-induced TNFR-related gene; GM-CSF, granulocyte macrophage colony-stimulating factor; gp100, glycoprotein 100; HLA, human lymphocyte antigen; HSP, heat shock protein; ICD, immunogenic cell death; IDO1, indoleamine 2,3-dioxigenase 1; IL, interleukin; LAG-3, lymphocyte activation gene-3; MAGE-A3, melanoma-associated antigen 3; MAPK, mitogen-activated protein kinase; MDSC, myeloid-derived suppressor cell; MHC, major histocompatibility complex; PD-1, programmed cell death-1; PD-L1, programmed cell death-1 ligand-1; TAMs, tumor-associated macrophages; TCR, T cell receptor; TIL, tumor-infiltrating lymphocyte; TIM-3, T cell immunoglobulin and mucin domain-3; Treg, regulatory T; VEGF, vascular endothelial growth factor.

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1. Introduction

Immunotherapy is considered an effective treatment for melanoma. This effectiveness is based on two mechanisms. First, melanoma develops in the skin, meaning that tumor cells are surrounded by antigen-presenting dendritic cells (DCs) such as Langerhans cells. Therefore, tumor-specific cytotoxic T lymphocytes (CTLs) are easily activated. Second, exposure to ultraviolet light damages the DNA of melanoma cells, thereby generating many different and highly immunogenic antigens [1,2]. Here, we divide immunotherapy for melanoma into four categories: 1) methods aimed at recovering the restrained function of T cells (known as brake release/immune checkpoint blockade); 2) methods aimed at activating tumor antigen-specific T cell responses (accelerators); 3) methods involved in the transfer of activated tumor-specific T cells; and 4) methods aimed at removing immunosuppressive factors within the tumor microenvironment. Furthermore, we discuss which type of immunotherapy should be administered based on the patients' immune response. Various trials of combination immunotherapy for melanoma are likely to be conducted in the near future. Thus, it is important to analyze the immune response occurring in each patient in detail, and to clarify the fundamental immune mechanism involved, if we are to bring melanoma under control.

2. Brake release/immune checkpoint blockade

Immune checkpoints are cell surface molecules that optimize the strength and quality of an immune response. The immune response is upregulated by stimulatory checkpoint molecules (e.g., CD28, OX-40, and 4-1BB) and downregulated by inhibitory checkpoint molecules (e.g., CTLA-4, PD-1, and LAG-3) (Fig. 1). Immune checkpoints play an essential role in immunological tolerance. Often, tumor cells circumvent the system and escape T cell surveillance. Therapeutic blockade of inhibitory checkpoint molecules favors T cell responses and enhances antitumor function (Fig. 2).

2.1. CTLA-4 and PD-1/PD-L1

Effector T lymphocytes (helper T cells and CTLs) recognize and destroy tumors. In general, T cell activation is regulated by two sequential signals: the T cell receptor (TCR) signal (T cells recognize tumor antigens via the TCR in conjunction with major histocompatibility complex (MHC) molecules expressed by antigen-presenting cells (APCs)), and the co-stimulatory/inhibitory signal. Immune checkpoint molecules regulate the interaction between the T cell and the APC. For example, the stimulatory checkpoint molecule CD28 on T cells binds to CD80 on the APC (Fig. 1). Following activation of the co-stimulatory signal via CD28, CTL-associated antigen 4 (CTLA-4), which is an inhibitory checkpoint molecule, is expressed on the T cell surface. CTLA-4 inhibits the co-stimulatory signal by competing with CD28 for binding to CD80 on the APC [3,4]. In addition, CTLA-4 suppresses T cell activation indirectly by activating $CD4^+/CD25^+/FoxP3^+$ regulatory T (Treg) cells, which are essential for peripheral immunological tolerance [5,6].

In March 2011, the U.S. Food and Drug Administration approved ipilimumab (an antibody that blocks CTLA-4) as an immune checkpoint blocker for the treatment of unresectable melanoma (Fig. 2). Data from ten prospective and two retrospective studies, including two phase III trials, reveal patients receiving the drug showed median overall survival rates of 11.4 months; the 3 year survival rate was 22% [7]. Furthermore, another study showed that

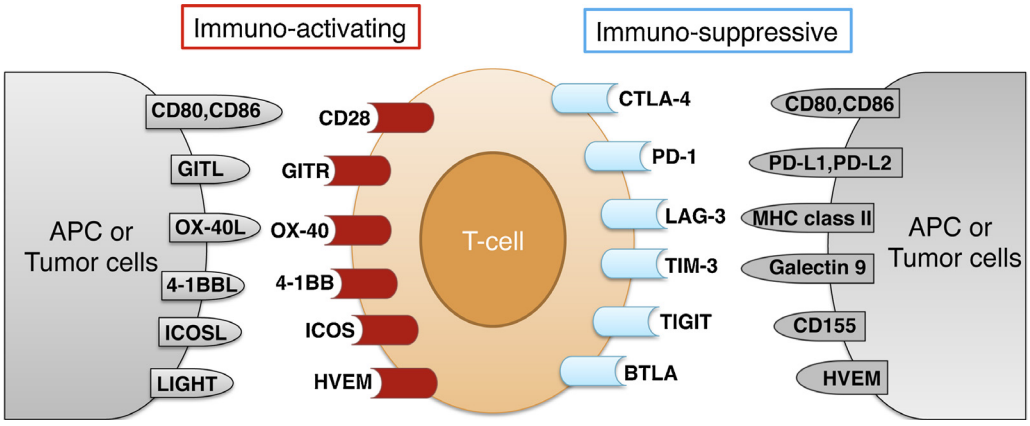

Fig. 1. Stimulatory and inhibitory checkpoint molecules expressed by immune cells and cancer cells. BTLA, B and T lymphocyte attenuator; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; GITL, glucocorticoid-inducible tumor necrosis factor ligand; GITR, glucocorticoid-inducible tumor necrosis factor receptor; HVEM, herpesvirus entry mediator; ICOS, inducible T cell co-stimulator; LAG-3, lymphocyte activation gene-3; LIGHT, homologous to lymphotoxin, exhibits inducible expression and competes with HSV glycoprotein D for binding to herpesvirus entry mediator, a receptor expressed on T lymphocytes; PD-1, programmed cell death-1; and TIGIT, T cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain.