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Review Article

Immune checkpoint inhibitors for nonsmall cell lung cancer treatment

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Abstract

Immune checkpoint inhibition with blocking antibodies that target cytotoxic T-lymphocyte antigen-4 (CTLA-4) and the programmed cell death protein 1 (PD-1) pathway [PD-1/programmed death-ligand 1 (PD-L1)] have demonstrated promise in a variety of malignancies. While ipilimumab has been approved as a CTLA-4 blocking antibody by the US Food and Drug Administration for the treatment of advanced melanoma, it is still not approved for lung cancer treatment. In contrast, nivolumab and pembrolizumab, both PD-1 blocking antibodies, have been approved for second-line treatment of nonsmall cell lung cancer in 2015 because of their high potency and long-lasting effects in some patient subgroups. Other PD-1 and PD-L1 monoclonal antibodies are also in active development phase. Treatment with such immune checkpoint inhibitors is associated with a unique pattern of immune-related adverse events or side effects. Combination approaches involving CTLA-4 and PD-1/PD-L1 blockade or checkpoint inhibitors with chemotherapy or radiotherapy are being investigated to determine whether they may enhance the efficacy of treatment. Despite many challenges ahead, immunotherapy with checkpoint inhibitors has already become a new and important treatment modality for lung cancer in the last decade following the discovery of targeted therapy.

Keywords: adenocarcinoma; checkpoint inhibitor; immunotherapy; lung cancer; lymphocytes

1. Introduction

Lung cancer is the leading cause of cancer-related deaths in Taiwan and other developed countries in the world. The 5-year survival rate was only 15.9%, with a median survival of 13.2 months, in Taiwan between 2002 and 2008.[1]

There are two arms of the immune system, the innate and the adaptive, which protect the body from foreign agents. The innate immune system includes physical epithelial barriers, phagocytes, natural killer cells, and circulating complement proteins. The innate immune system is the first line of defense against pathogens. In contrast, the adaptive arm of the immune system is dormant until it is primed by the presence of a pathogen that has evaded or overwhelmed the innate immunity. Components of the adaptive immune system include both B cells and T cells. Naïve B cells are activated to produce antigen-recognizing antibodies when they are presented with antigens from a pathogen. When foreign antigens are presented to naïve T cells, they mature into one of two types of effector T cells: $CD4^+$ helper T cells that facilitate antibody production, and $CD8^+$ cytotoxic T cells that directly kill cells recognized as foreign (such as viral infected cells or tumor cells); this process is called cell-mediated immunity. The adaptive immune response is initiated when tumor cell antigens released by innate immunity are taken up by dendritic cells. These dendritic cells then migrate to the draining lymph nodes, where they present these tumor antigens to T cells, causing them to mature into cytotoxic T cells to destroy tumor cells (Fig. 1).

Conflicts of interest: The author declares that he has no conflicts of interest related to the subject matter or materials discussed in this article.

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Although the immune system plays an important role in recognizing, controlling, and eradicating cancer, cancer induces immunosuppression through several mechanisms that may suppress effective antitumor immunity, including but not limited to: (1) secretion of immunosuppressive cytokines; (2) loss of major histocompatibility complex antigen expression; (3) and programmed cell death protein 1/programmed cell death protein 1 ligand (PD-1/PD-L1) interaction of tumor cells with immune cells.[2−6] In the past, immunotherapy has had minimal success in lung cancer treatment, which was attributed in part to the belief that lung cancer is non-immunogenic.[7−11] Most patients present with advanced disease and are immunosuppressed, as documented by decreased lymphocyte counts and cytotoxic function seen in this patient population.[8,11−13] Regulatory T-cells ($CD4^+$ Treg) are a subpopulation of lymphocytes that play an important role in suppressing tumor immune surveillance, and have been found to have higher levels in peripheral blood and tumor microenvironment of lung cancer patients compared with other T-cell subpopulations.[14] $CD4^+$ Treg suppress cytotoxic T-cell functions that are responsible for killing tumor cells. We previously also showed that double signal stimulation is needed for these immunosuppressed lymphocytes to recover their cytotoxic function against tumor cells.[9,15−18]

It was recently found that cancer cells can prevent themselves from immune surveillance and killing through adaptive immune resistance, causing the disabling of tumor-specific T cells (Fig. 2).[19,20] Many types of cancers have been found to express PD-L1 on their tumor cell surfaces, which is a known ligand of the PD-1 receptor on T cells. This pathway of interaction between PD-1 and PD-L1 causes T-cell downregulation and functional inhibition.[5,6] There are two immune checkpoint inhibitory pathways that involve signaling through CTLA-4 or PD-1 with their ligands (Figs. 1 and 2). Antibody therapies against these negative immunologic regulators have demonstrated significant success in lung cancer treatment in recent years. This review focuses on antibodies that block the CTLA-4 and PD-1/PD-L1 pathways. We discuss the preclinical rationale and clinical experience with these antibodies in nonsmall cell lung cancer (NSCLC) treatment.

2. Cytotoxic T-lymphocyte antigen-4 pathway

Cytotoxic T-lymphocyte antigen-4 (CTLA-4) is a receptor that is expressed on the T-cell surface during the T-cell activation phase. Activation of the T-cell requires both antigen presentation in the context of a major histocompatibility complex molecule and a costimulatory signal stimulation by B7 from an antigen-presenting cell to interact with CD28 on the T-cell. Early after T-cell activation, CTLA-4 is translocated to the plasma membrane of the T-cell. CTLA-4 binds members of the B7 family with a much higher affinity than CD28, where it downregulates the function of activated T-cells (Fig. 1). CTLA-4 downregulates activated T-cell function not only through preventing costimulation by outcompeting CD28 for its ligand, B7, but also by inducing T-cell cycle arrest.[21−24] Through these mechanisms, CTLA-4 has an essential role in maintaining normal immunologic homeostasis, as evidenced by the fact that mice deficient in CTLA-4 died from fatal lymphoproliferative disease.[25]

CTLA-4 also regulates tumor immunity via Treg that expresses high levels of surface CTLA-4. CTLA-4-expressing

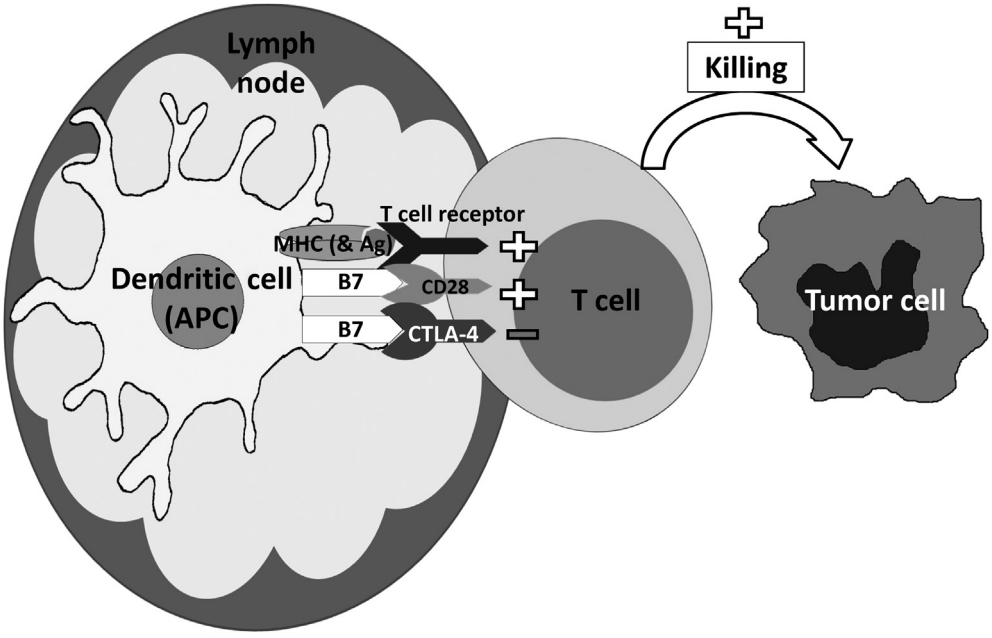

Fig. 1. T-cell activation phase and the cytotoxic T-lymphocyte antigen-4 (CTLA-4) immunologic checkpoint. T-cell activation requires antigen presentation in the context of a major histocompatibility complex (MHC) molecule in addition to the costimulatory signal stimulation when B7 on an antigen-presenting cell interacts with CD28 on a T cell. Soon after activation, CTLA-4 is translocated to the plasma membrane where it downregulates the function of T cells to maintain immunologic homeostasis.