Non–Small-Cell Lung Cancer

Role of the Immune System and Potential for Immunotherapy

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Abstract: As the leading cause of cancer death worldwide, lung cancer continues to impose a major burden on healthcare systems and cause significant challenges for clinicians and patients. Most patients present with advanced disease at the time of diagnosis and have a poor prognosis, with the vast majority surviving less than 5 years. Although new therapies have been introduced in recent years that target molecular disease drivers present in a subset of patients, there is a significant need for treatments able to improve response and extend survival while minimizing effects on quality of life. Recent evidence of clinical efficacy for immunotherapeutic approaches for lung cancer suggests that they will become the next major therapeutic advance for this disease. Non–small-cell lung cancer, which accounts for approximately 85% of lung cancer cases, has historically been considered a nonimmunogenic disease; however, as with several other malignancies, recent data show that much of this lack of immune responsiveness is functional rather than structural (i.e., possible to overcome therapeutically). This review explores the key elements of the immune system involved in non–small-cell lung cancer and briefly examines immunotherapeutic strategies in development to shift the balance of immune activity away from a tumor-induced immune-suppressive state toward an active antitumor immune response.

Key Words: Non–small-cell lung cancer, Immune system, Immunotherapy, Checkpoint inhibitors, Cancer vaccines.

(*J Thorac Oncol.* 2015;10: 974–984)

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Disclosure: David P. Carbone was a paid consultant for Boehringer-Ingelheim, Bristol-Myers Squibb, Clovis, Genentech, Novartis, and Pfizer, and is currently receiving research grants from Bristol-Myers Squibb. David R. Gandara is currently receiving research grants from Bristol-Myers Squibb and Merck. Scott J. Antonia is currently a paid consultant for Bristol-Myers Squibb and is currently receiving research grants from MedImmune. Luis Paz-Ares is currently a paid consultant for Bristol-Myers Squibb. Christoph Zielinski is an ongoing paid consultant for Bristol-Myers Squibb. No financial support or compensation was received by the authors for this publication.

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DOI: 10.1097/JTO.0000000000000551

ISSN: 1556-0864/15/1007-0974

Lung cancer is the leading cause of cancer-related death worldwide, claiming an estimated 1.59 million lives in 2012.[1] Non–small-cell lung cancer (NSCLC) is the predominant form of the disease, accounting for approximately 85% of cases.[2] The majority of patients present with locally advanced or metastatic disease, and many do not survive more than 5 years beyond diagnosis.[2,3] Although targeted therapy has produced real benefit for specific molecular subtypes of NSCLC, traditional chemotherapy, which usually provides short-lived benefit, remains the only option for most patients. Consequently, there remains a major need for therapy that significantly extends patient survival without compromising quality of life.

In recent years, there has been an increasing recognition of the role of the immune system in cancer development and progression,[4–6] with a corresponding focus on utilizing immunotherapy in the clinic and regulatory approvals of immunotherapy for renal cell cancer (interleukin [IL]-2 and interferon-α[7]), prostate cancer (sipuleucel-T[8]), and melanoma (ipilimumab,[9] nivolumab,[10] pembrolizumab[11]). Although NSCLC has historically been considered a nonimmunogenic disease, emerging evidence has demonstrated that the lack of an effective immune response is in fact often the result of specific, active immune-evasive mechanisms, which if understood can be overcome therapeutically with significant clinical efficacy. Harnessing this potential has therefore become a primary area of clinical interest.[12–14] Given the increasing understanding of the role of immunology in oncology, this article examines the key elements of the immune system involved in cancer in general and in NSCLC specifically, and briefly outlines some of the immunotherapeutic strategies currently being developed to improve patient outcomes.

THE IMMUNE SYSTEM AND CANCER

The Antitumor Immune Response

The immune system is now recognized to have the potential to destroy cancer cells and inhibit tumor growth through responses elicited by its innate and adaptive arms.[15] Innate immune responses are antigen nonspecific, develop quickly, and are mediated by various effector cells (natural killer [NK] cells, polymorphonuclear leukocytes, and mast cells, as well as antigen-presenting cells (APGs), such as macrophages and dendritic cells [DCs]), which lead to the secretion of interferon gamma (IFN-γ) and perforin, as well as inflammatory

cytokines that induce apoptosis of tumor cells.[4] In contrast, adaptive immune responses are antigen specific, develop more slowly, offer immune memory, and comprise both humoral and cellular immunity mediated by B and T cells, respectively.[15,16] In this respect, adaptive rather than innate immunity offers the greatest potential for durable, robust anticancer immune responses. Of note, some of the cells involved in innate immunity, such as DCs, macrophages, and NK cells, also play a role in adaptive immunity.[4]

The adaptive anticancer immune response is initiated by immature DCs, which are found in most human tumors and are capable of capturing antigens released from cancer cells (Fig. 1).[17,18] After maturation (activation), DCs present tumor antigens within major histocompatibility complex (MHC) molecules to naïve T cells in the tumor-draining lymph nodes, triggering a protective T-cell response composed of specific CD4+ helper T (Th) cells and CD8+ cytotoxic T cells. T-cell activation requires interaction not only between the antigen–MHC complex on DCs and T-cell receptors but also among an array of co-stimulatory molecules, including CD80/86 on DCs and the CD28 receptor on T cells. After infiltrating the tumor, activated cytotoxic T cells are capable of recognizing and killing tumor cells directly in an MHC-restricted fashion. In addition, activated Th cells secrete cytokines that induce inflammation and recruit other immune cell populations to the tumor microenvironment to eliminate cancer cells. DCs may also induce B-cell-mediated antibody responses and NK cell activity.

Promotion of Tumor Growth by the Immune System

Insights into cellular and molecular immunologic processes have revealed that the immune system is capable of not only inhibiting but also promoting tumor growth, through either the selection of tumor cells that are better able to survive in an immunocompetent host or the creation of conditions within the tumor microenvironment that facilitate tumor growth.[5,6] It has been proposed that this dual host-protective and tumor-promoting role results from a dynamic relationship between cancer cells and the immune system termed "immunoediting," which consists of three distinct phases: elimination, equilibrium, and escape (Fig. 2).[15] In the elimination phase, acute immune responses, both innate and adaptive, recognize and destroy cancer cells (through a process termed "immunosurveillance") before they develop into a clinically detectable tumor.[5,6,15] Early evidence suggested that premalignant clones expressing novel somatic mutant epitopes (immunogenic portions of antigens) might be targeted by the immune system in the initial stages of tumor development.[19] Tumor clones that escape the elimination phase remain dormant in the subsequent equilibrium phase, during which tumor growth does not occur but the immunogenicity of the tumor cells continues to be shaped by selective immune pressure from the adaptive immune response.[6,15] In time, changes arising in the tumor cell population caused by this selective pressure and/or changes in the immune system as a result of prolonged tumor-mediated immunosuppression may lead to immune escape and tumor growth.[6,15]

Tumor cells entering the immune escape phase are able to create an immunosuppressive state within the tumor microenvironment by subverting the same mechanisms that under normal conditions help regulate the immune response and prevent damage to healthy tissue.[6] Key immunosuppressive cell types found in the tumor microenvironment are regulatory T (T_{reg}) cells, myeloid-derived suppressor cells (MDSCs), and tumor-associated macrophages.[6,17,20] T_{reg} cells, which are positive for CD4, CD25, and the Foxp3 transcription factor, suppress the function and proliferation of tumor-specific CD4+ and CD8+ T cells and NK cells, whereas MDSCs induce T_{reg} cells and limit effector T-cell proliferation by means of the production of various immunosuppressive molecules.[6,17] Tumor-associated macrophages and stromal cells may also secrete cytokines that inhibit an adaptive immune response, such as IL-10 and transforming growth factor-β (TGF-β).[16,20] In addition, both tumor cells and other cells present in the tumor microenvironment may express the immunosuppressive enzyme indoleamine-2,3-dioxygenase, which depletes the amino acid tryptophan

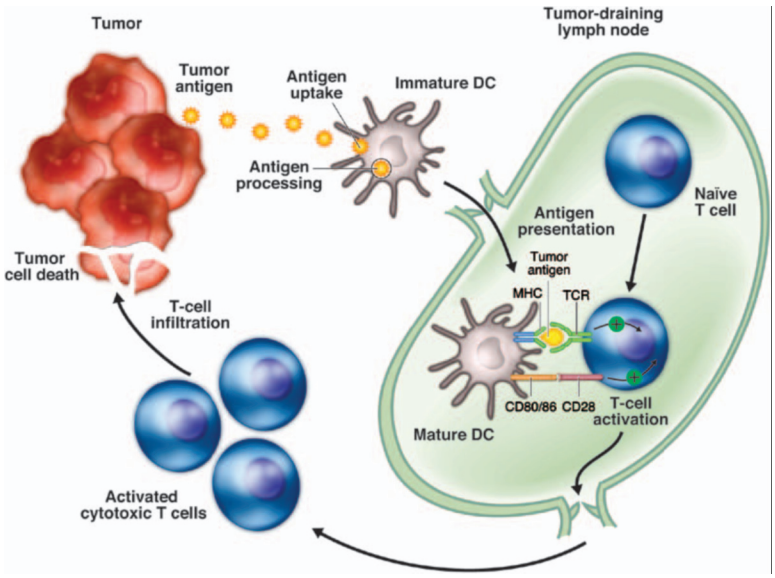

FIGURE 1. Adaptive anticancer immunity. The adaptive anticancer immune response is initiated by immature DCs, which capture and process tumor antigens. DCs subsequently undergo maturation and migrate to tumor-draining lymph nodes, where they present tumor antigens within MHC molecules to naïve T cells, triggering a protective T-cell response. T-cell activation requires interaction not only between the antigen–MHC complex on DCs and TCRs but also among an array of co-stimulatory molecules, including CD80/86 on DCs and the CD28 receptor on T cells. The adaptive anticancer immune response culminates with the infiltration of activated cytotoxic T cells into the tumor, killing cancer cells. DC, dendritic cell; MHC, major histocompatibility; TCR, T-cell receptor.