Tumor Microenvironment Characteristics and Innovative Immunotherapeutic Methods for Non-Small Cell Lung Cancer

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Abstract

Immune checkpoint inhibitor immunotherapy has transformed the treatment of Non-Small Cell Lung Cancer (NSCLC). Although monoclonal antibodies against programmed cell death-1 (PD-1) and PD-ligand 1 (PD-L1) are commonly employed in clinical practice, additional antibodies that can overcome innate and acquired resistance are expected to undergo preclinical and clinical trials. Tumor cells, on the other hand, can create and enhance the tolerogenic character of the Tumor Microenvironment (TME), leading to tumor growth. As a result, the immune escape mechanisms exploited by growing lung cancer involve a delicate interplay between all TME actors. A deeper understanding of the molecular biology of lung cancer, as well as the cellular/molecular mechanisms involved in the interaction between lung cancer cells and immune cells in the TME, could lead to the identification of new therapeutic weapons in the long-running battle against lung cancer. This article explores the role of TME in lung cancer progression and identifies potential advances and pitfalls of immunotherapy for NSCLC.

Keywords: Tumor microenvironment •Immunotherapy • Immune checkpoint inhibitor • Non-small cell lung cancer

Introduction

Lung cancer is the greatest cause of cancer death in the world1, with non-small cell lung cancer (NSCLC) being the most common pathological form. Monoclonal antibodies against programmed cell death-1 (PD-1) and its ligand (PD-L1), as well as cytotoxic T lymphocyte antigen 4 (CTLA-4) have ushered in a new age of NSCLC treatment. Nonetheless, there has been non-responsiveness and long-term resistance. Tumor cells can generate and promote the tolerogenic character of the tumor microenvironment (TME), resulting in immune evasion and tumor development. A deeper knowledge of the cellular/molecular mechanisms involved in the interplay of all TME actors could lead to the identification of new therapeutic weapons in the long-running struggle against lung cancer. In this section, we explore the characteristics of TME in NSCLC and identify potential advances and obstacles [1-4].

The TME is a dynamic and complicated network in which immunosuppressive cells, secretory chemicals, and signaling pathways all play important roles in immune tolerance and tumor growth. Chronic inflammatory conditions may cause immune cell differentiation to be deviated or altered in lung cancer, resulting in a reduced antitumor response and resistance to Immune Checkpoint Inhibitors (ICIs).

TIL density, distribution, and characteristics are important in predicting clinical outcomes for ICI treatment in lung cancer. TIL subsets with effector (anti-tumor) and uppressive (pro-tumor) characteristics are found in the primary TIL populations (CD4, CD8, and CD19/20). Their function is influenced by their surroundings, and the balance between them determines the immune status and progression of lung cancer.

In lung cancer, higher CD8+ T cell density is related with better Overall Survival (OS). The primary Cytotoxic T Lymphocytes (CTLs) are 4 CD8+ T cells, which mediate antitumor immunity by recognizing the major histocompatibility complex class I (MHC-I) molecules on the surface of tumor cells. 5 CTL-mediated antitumor immunity, on the other hand, is functionally limited by a number of mechanisms. The loss of expression of MHC-I molecules, achieved by tumor cells via down-regulation of the antigen process and peptide antigen presentation on MHC molecules, can directly prevent CD8+ T cell antigen recognition.

Tumor cells can increase the expression of Indoleamine-2,3-Dioxygenase (IDO) by depriving TME of the necessary amino acids tryptophan and arginine. 8 It has been demonstrated that combining IDO inhibitors with ICIs boosted the number and function of CD8+ T cells in the TME. 9 Tumor cells with fast growth also have significant glycolytic activity, resulting in limited glucose availability for intratumoral CD8+ T cells. 10 Because of the absence of glucose, this process inhibits the proliferative ability and effector functions of CD8+ T lymphocytes, such as the production of proinflammatory interferon-gamma (IFN-). 11 Finally, tumor cells and immune cells in the TME can activate immune checkpoint signaling involving multiple inhibitory co-stimulatory molecules, resulting in serious flaws in tumor cell proliferation, migration, and cytokine secretion.

PD-1, CTLA-4, T cell immunoglobulin and mucin-domain containing 3 (TIM-3) and Lymphocyte-Activation Gene 3 (LAG-3) are the most well-studied inhibitory receptors. 13, 14, 15, 16 Dysfunctional, "burned-out" CD8+ TILs (Ebo) with strong proliferation and activation markers but poor IFN production were recently found. Importantly, these cells with elevated PD-1, LAG-3, and TIM-3 expression were linked to ICI resistance. 17 During the progression of NSCLC, there is a gradual and continuous upregulation of these alternative immune checkpoint receptors on intratumoral CD8+ T cells. 18 Furthermore, a recent study found that CD8 and PD-L1 double-positive T cells were associated with increased tumor burden, resulting in a "hot" but immunosuppressive TME. As a result, elevated TIL levels may affect neoantigen recognition rather than immunosuppression or malfunction. Patients with these features, on the other hand, had a higher risk of responding well to PD-1 inhibitors. 19 Interestingly, T cells from cancer patients who responded differently to immunotherapy had different genetic characteristics. Responders primarily expressed genes associated with higher memory and effector functions, whereas non-responders expressed genes associated with T cell dysfunction. In the TME, Tregs are an immunosuppressive subtype of CD4+ T cells. Foxp3+ Treg infiltration was associated with a poor outcome in several cancer types, indicating a protumoral effect. CTLA-4 and CD25 are important immunosuppressive molecules expressed on Tregs.CTLA-4 inhibits CD80/86 expression on Antigen-Presenting Cells (APCs), resulting in reduced activation of conventional T cells. CD25 binds to IL-2 with high affinity, resulting in lower levels of IL-2 in the surrounding environment, reducing IL-2-dependent T cell activation and proliferation. 24 Furthermore, Tregs produce suppressive cytokines and molecules such as TGF-, IL-10, IL-35, and adenosine, which inhibit the expansion and function of effector cells and disrupt cell metabolism.

Tregs also upregulate B7-H4 and IDO to decrease APC function in TME and inhibit angiostatic cytokines produced by effector T cells such as IFN,

which contributes to tumor angiogenesis. Furthermore, direct cytolysis of Tregs via mediators such as galectin-1 and granzyme B causes effector cell death. Several factors influence Treg recruitment in TME. *CCL22* generated by tumor macrophages and tumor cells can recruit CCR4-expressing Tregs to the tumor site. Tumor cells can recruit *CCR10+* Tregs by the production of *CCL28* [5-8].

TLS in the TME is a prognostic factor for the majority of solid tumors. The presence of its distinct subpopulations or dynamics during therapy can predict anti-PD-1 response in NSCLC. A mature TLS is primarily composed of a segregated T cell zone with mature dendritic cells (DCs) adjacent to a B cell follicle with a germinal center. In this structure, the presentation of adjacent tumor antigens by DCs, (re-)activation of naive or memory lymphocytes, and the generation of effector cells are all easily accomplished without the migration of random TILs into the tumor bed. Tumor-infiltrating B cells (TIL-Bs) can be seen in the TME at all stages of development and are typically found at the invasive margin. Although TIL-Bs is seen in just a small percentage of individuals with a specific tumor, they have a favorable impact on clinical outcomes when they are numerous. An in vitro assay revealed that TIL-Bs act as local APCs, providing secondary stimulation to CD4+ TILs in NSCLC, causing them to change phenotype and function. Activated TIL-Bs and antigen-associated B cells elicited the effector T cell response, whereas exhausted TIL-Bs elicited the Treg phenotype. In NSCLC, a positive connection between TLS-Bs density and CD4+ T cell receptor (TCR) clonality was observed,44 implying that active interaction between T and B cells in TLS could stimulate the proliferation of selective T cell clones. Furthermore, TIL-Bs efficiently produce IgG and IgA against tumor-specific antigens in NSCLC, including LAGE-1, MAGE family, P53, and NY-ESO-1, indicating the presence of a humoral immune response in NSCLC.

Angiogenesis with physically and functionally abnormal vasculature is a significant component of the TME in lung cancer. VEGF and its receptor not only increase vascular permeability by regulating the proliferation, differentiation, and migration of microvessel endothelial cells, but they also suppress the functions of effector immune cells such as CD8+ T cells, NKs, and DCs while facilitating the suppressive effect of Tregs, TAMs, and MDSCs. As a result, combining antiangiogenic therapy with immunotherapy makes sense. Several clinical trials in various settings have evaluated this combination in NSCLC.

The TME of NSCLC with oncogenic driver mutations may be unique and dynamic, influenced by both the particular mutation and targeted therapy, resulting in anti-tumor immune responses that differ from those of the wildtype. For example, epidermal growth factor receptor (EGFR) sensitive mutations have a low tumor mutation burden or neoantigen load, which indicates lower tumor immunogenicity and noninflamed TME. Through interferon regulatory factor-1, 144 *EGFR* mutations can downregulate *CXCL10* and *CCL5*, resulting in decreased CD8+ T cell invasion. Instead, it activates *CCL22* via cJun/cJun N-terminal kinase, resulting in Treg recruitment. Exosomes containing EGFR stimulate DCs to create IDO, which is required for the conversion of CD4+ T cells to Tregs.

Conclusion

TME plays an important role in the progression and development of lung cancer. TME immune components interact with tumor cells in a complex and multidimensional manner, eventually defining the tumor's fate. Importantly, because lung cancers are very diverse, transcriptional and epigenetic changes in lung cancer cells contribute to TIL depletion phenotypes. Immunotherapy based on ICIs has been shown to be effective in the treatment of lung cancer. However, it only targets a specific phase of anti-cancer immunity and frequently fails against a "cold" TME phenotype characterized by the absence of tumor-specific T cell priming and TILs.255 As a result, more combination strategies are required in this war against lung cancer to mobilize all components involved in all stages of anti-tumor immunity.

Immunotherapy for lung cancer is becoming more diverse, inventive, and personalized, thanks to ongoing basic and revolutionary research. Better results have been seen with reasonable combinations of ICIs and conventional treatment. Inhibitors that target alternative immune checkpoint molecules are also on the rise. Because TME components play a key role in many steps of tumor immunity cycles and may serve as a complement to immune checkpoint molecules, they will be interesting targets for immunotherapy of lung cancer to overcome ICI resistance. Under emerging immunotherapy strategies, lung cancer will gradually evolve into a chronic disease in the near future.

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