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PDL1 in Cancer: A Remarkable Mile Stone Achieved

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Editorial

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Abbreviation: NSCLC: Non-Small Cell Lung Cancer.

Editorial

PD-1, or programmed cell death protein 1, is indeed a critical immune checkpoint receptor expressed on activated T lymphocytes, including tumor-specific CD4+ helper and CD8+ killer T cells. Originally, PD-1 was identified as a regulator of cell death, but its role in immune regulation has since been recognized as crucial in the context of cancer immunotherapy. When PD-1 binds to its ligands, primarily PD-L1 and PD-L2, which are often overexpressed on tumor cells and other immune cells within the tumor microenvironment, it down regulates T cell activity and contributes to immune evasion by tumors. This interaction suppresses the cytotoxic function of T cells, allowing tumors to evade immune surveillance and continue to grow unchecked [1].

However, therapeutic antibodies that block the PD-1/PD-L1 interaction can disrupt this immune checkpoint pathway, effectively restoring the cytotoxic activity of T cells against tumor cells. By inhibiting PD-1 or PD-L1, these antibodies enhance the immune system's ability to recognize and eliminate cancer cells, leading to improved antitumor responses and clinical outcomes in many cancer types. The blockade of PD-1 or PD-L1 has revolutionized cancer treatment and has become a cornerstone of immunotherapy in various malignancies. By restoring host immunity against the tumor, PD-1/PD-L1 checkpoint inhibitors have demonstrated remarkable efficacy and durable responses in a subset of cancer patients, leading to their widespread use in clinical practice [2].

Definition of PD-1/PD-L1

PD-1, also known as programmed cell death protein 1 or CD279, belongs to the immunoglobulin superfamily and is primarily expressed on the surface of activated T cells, particularly CD4+ helper T cells and CD8+ cytotoxic T cells. [3] PD-L1, or programmed death-ligand 1, also known as CD274, is a transmembrane protein that serves as the main ligand for the PD-1 receptor. PD-L1 is expressed on a variety of cell types, including antigen-presenting cells such as dendritic cells and macrophages. Additionally, PD-L1 is constitutively expressed by non-lymphoid tissues, including the heart, lung, and other organs [4].

The binding of PD-L1 to PD-1 on activated T cells results in the inhibition of T cell function. This interaction serves as a crucial mechanism for negative feedback control of inflammation and autoimmunity during the peripheral effector phase of T cell activation. By inhibiting the activity of activated T cells, PD-L1 helps to regulate the immune response and prevent excessive tissue damage in response to infection or injury [5].

Tumor cells can exploit the PD-1/PD-L1 pathway to evade the immune system's attack. PD-1 (programmed cell death protein 1) is a receptor found on the surface of T cells, which are a type of immune cell. PD-L1 (programmed death-ligand 1) is a protein expressed on the surface of various cells, including tumor cells. When PD-L1 on tumor cells binds to PD-1 on T cells, it sends a signal to the T cell to become inactive or "exhausted," preventing it from attacking the tumor cells effectively. This mechanism helps the tumor cells evade the immune response and continue to grow unchecked. Immunotherapies targeting the PD-1/PD-L1 pathway, such as checkpoint inhibitors, aim to block this

interaction, thereby restoring T cell activity and enabling the immune system to recognize and attack the tumor cells [6].

Drugs Targeting PD-1/PD-L1 Pathway

Several drugs targeting the PD-1/PD-L1 pathway have been developed and approved for the treatment of various types of cancer. Some of the key ones include:

Pembrolizumab (Keytruda): A monoclonal antibody that targets PD-1. It has been approved for the treatment of several types of cancer, including melanoma, non-small cell lung cancer, head and neck squamous cell carcinoma, classical Hodgkin lymphoma, urothelial carcinoma, and others.

Nivolumab (Opdivo): Another monoclonal antibody targeting PD-1. It has been approved for the treatment of melanoma, non-small cell lung cancer, renal cell carcinoma, classical Hodgkin lymphoma, squamous cell carcinoma of the head and neck, and others.

Atezolizumab (Tecentriq): A monoclonal antibody targeting PD-L1. It has been approved for the treatment of non-small cell lung cancer, small cell lung cancer, urothelial carcinoma, triple-negative breast cancer, and others.

Durvalumab (Imfinzi): Another monoclonal antibody targeting PD-L1. It has been approved for the treatment of unresectable stage III non-small cell lung cancer and extensive-stage small cell lung cancer

Avelumab (Bavencio): Is another monoclonal antibody that targets PD-L1. It is approved for the treatment of several types of cancer. Avelumab works by binding to PD-L1 on tumor cells and blocking its interaction with PD-1 on T cells, thereby restoring the T cell-mediated immune response against the tumor. It has been approved for treatment of Metastatic Merkel cell carcinoma, Locally advanced or metastatic urothelial carcinoma and Advanced renal cell carcinoma [7].

PD-L1 as a Predictive Biomarker

PD-L1 expression on tumor cells has been investigated as a predictive biomarker for response to PD-1/PD-L1 checkpoint inhibitors in various cancers. The rationale behind using PD-L1 expression as a biomarker is that tumors with higher levels of PD-L1 may be more likely to respond to PD-1/PD-L1 blockade [8]. However, the role of PD-L1 expression as a predictive biomarker is complex and varies depending on the cancer type, treatment setting, and specific drug being used. Here are some key points regarding PD-L1 as a predictive biomarker:

Response Prediction: In some cancers, higher levels of PD-L1 expression on tumor cells have been associated with better response rates to PD-1/PD-L1 inhibitors. Patients with PD-L1-positive tumors may have a higher likelihood of responding to treatment compared to those with PD-L1-negative tumors.

Tumor Heterogeneity: PD-L1 expression can be heterogeneous within tumors and may change over time or in response to treatment. Therefore, a single biopsy sample may not capture the full spectrum of PD-L1 expression within a tumor.

Tumor Type-Specific: The utility of PD-L1 expression as a predictive biomarker varies across different cancer types. For example, PD-L1 expression is commonly used as a biomarker in non-small cell lung cancer (NSCLC) and urothelial carcinoma, but its predictive value may be less clear in other cancers.

Treatment Setting: The significance of PD-L1 expression as a predictive biomarker may differ depending on the treatment setting (first-line vs. second-line or beyond) and the specific drug being used.

Complementary Biomarkers: PD-L1 expression is just one of several biomarkers being investigated in the context of immune checkpoint inhibitor therapy. Other factors, such as tumor mutational burden, presence of tumor-infiltrating lymphocytes, and molecular signatures, may also influence treatment response.

Overall, while PD-L1 expression can provide valuable information in guiding treatment decisions, its predictive value is not absolute, and clinical decisions should be made based on multiple factors, including clinical trial data, patient characteristics, and tumor biology. Ongoing research aims to refine the use of PD-L1 and other biomarkers to optimize patient selection for immune checkpoint inhibitor therapy [9].

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