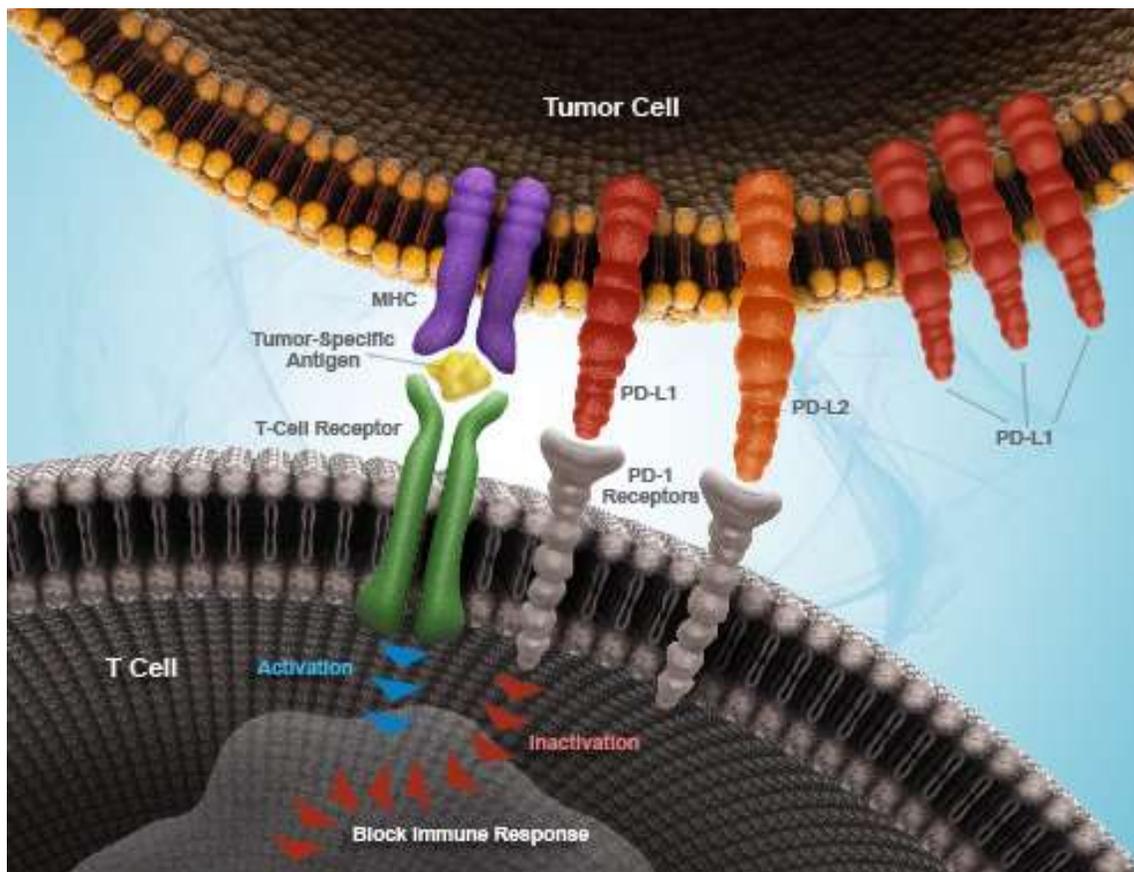


Tumor cells may evade the body's immune response by exploiting the PD-1 checkpoint pathway^{1,2}

- Emerging research has identified PD-1 as an immune checkpoint pathway that tumor cells may exploit to evade immune surveillance.^{1,3}
- Tumor cells may block immune responses via the PD-1 immune checkpoint pathway by expressing the dual PD-1 ligands PD-L1 and PD-L2.³⁻⁶
- PD-L1 and PD-L2 engage the PD-1 receptor on T cells in order to inactivate T cells, which may allow tumor cells to evade immune response.^{2,3,7,8}

Engagement of the PD-1 receptor by its ligands PD-L1 and PD-L2 may downregulate T-cell activity in the tumor microenvironment^{1-4,7}



MHC= major histocompatibility complex.

- PD-L1 is expressed on many tumor cells and may downregulate tumor-specific T-cell activity by binding to PD-1 in the tumor microenvironment.^{3,4,7}
- PD-L2 may also have a role in helping tumor cells evade the immune response.^{7,9}

PD-L1, an immune checkpoint ligand, is a potential predictive biomarker expressed on many tumor cells¹

- PD-L1 is expressed on tumor cells and may downregulate T-cell activity by binding

to the PD-1 receptor in the tumor microenvironment.¹

- PD-L1 is expressed on tumor cells in many different types of cancer.¹
- The potential of PD-L1 as a biomarker has become a focus of cancer research, as several studies indicate that PD-L1 expression may have predictive value.¹

PD-L1 expression by tumor type^{1,a}

Tumor type	% of tumor samples expressing PD-L1
Melanoma	38%–100%
Renal cell carcinoma	14%–54% ^b
Non-small cell lung cancer	21%–95% ^c
Bladder	20%–37% ^d
Head and Neck	31%–66%
Cervical	19%–29%
Glioblastoma multiforme	25%–45%
Breast	18%–59% ^e
Gastric	42%
Esophageal	20%–44% ^f
Hepatocellular carcinoma	15%–25%
Pancreatic	39%
Colorectal	21%–56% ^g
Thymic	88%–100% ^h
Ovarian	87%–89%
Sarcoma	12%–27% ⁱ
Acute myeloid leukemia	37%
Leukemias	57%
B-cell lymphomas	58%
Multiple myeloma	93%

Adapted from *Mol Cancer Ther.*, 2015, 14(4):OF3, Patel SP, Kurzrock R. PD-L1 expression as a predictive biomarker in cancer immunotherapy, with permission from AACR

^aData represent expression in tumor type based on various PD-L1 detection antibodies, assays, and cutoffs

for the definition of positivity. ^b54% represents metastatic specimens. ^c21% represents squamous only.

^d37% represents squamous only. ^e59% represents triple negative breast cancer only. ^f44% represents squamous only. ^g21% represents microsatellite stable only. 56% represents microsatellite instability high level only. ^hThymic carcinomas and thymomas. ⁱ27% represents gastrointestinal stromal tumors (GIST).

Analyses of biomarker expression can help contribute to a better understanding of an individual patient's tumor²

- PD-L1 expression on tumor cells may indicate tumor-induced inhibition of immune responses.¹
- Immunohistochemical analyses demonstrate that PD-L1 is expressed at varying levels on tumor cells.¹
- PD-L1 positive staining in a tumor specimen can be defined from 1% to 100% of tumor cells.¹

PD-L1=programmed death receptor-1 ligand 1; PD-1=programmed death receptor-1.

Oncology Meets Immunology: The Cancer–Immune System Connection

INTRODUCTION

Advancements in immunology have increased our understanding of the vast power of the immune system and its relevance to cancer. This FAQ Guide has been prepared in an effort to build on that critical understanding and answer a number of frequently asked questions about cancer, the immune system, and its antitumor capacity, as well as mechanisms that may be utilized by tumors to evade the body's immune response.

QUESTION 1. Why is immunology a focus in oncology research?

Preclinical and clinical evidence increasingly indicates that the fields of immunology and oncology are converging. Emerging research indicates that our own immune system may be an important ally in the fight against cancer. The body's immune response, through activated T cells and other mechanisms, might detect and destroy tumor cells, and protect against metastases.^{1,2}

The potential role of the immune system as a defensive mechanism against cancer has been hypothesized in part based on population-based studies of patients with disabled immune systems. Patients who present with human immunodeficiency virus infection,³ and transplant patients on long-term immunosuppressant therapies show an increased risk for developing certain types of cancer.⁴

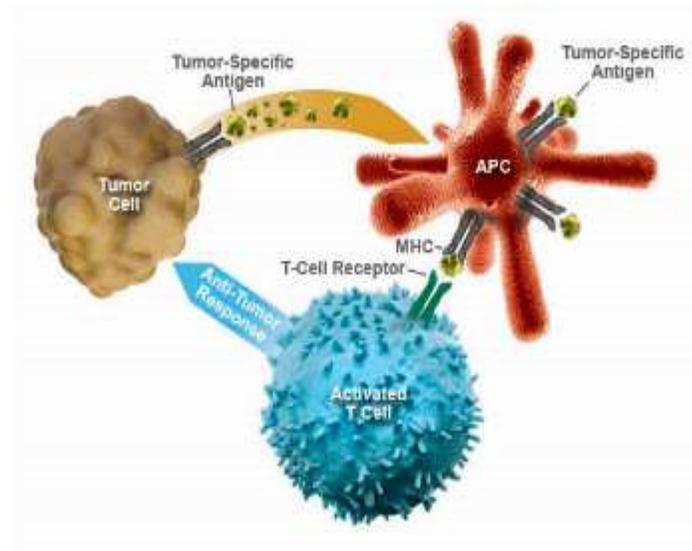
QUESTION 2. Tumor cells are not infectious pathogens. So, how does the immune system detect and destroy them?

The key to the ability of tumors to elicit an immune response is similar to that which occurs with infectious pathogens. Cancer cells express multiple antigens that are not expressed in normal tissue; therefore, some tumor cells can be detected and discriminated from normal tissue by the immune system, resulting in the initiation of an immune response. For instance, the body's immune response can detect tumor antigens and destroy the tumor cells through activated T cells.^{5,6} The antitumor response involves the same mechanisms as those involved in the destruction of pathogens.²

Antigens expressed by tumors are captured by antigen-presenting cells (APCs), such as dendritic cells.^{2,7} APCs carry the tumor-derived antigens to lymph nodes and present them to other immune cells, including cytotoxic T cells. When presented with tumor-derived antigens, naïve, cytotoxic T cells are activated (referred to as the initial or priming phase of activation) and travel back to the tumor. In the tumor microenvironment, activated T cells exert their cytotoxic actions, resulting in the destruction of cancer cells (known as the effector phase) (Figure 1).²

Oncology Meets Immunology: The Cancer–Immune System Connection

Figure 1. Tumor cell proliferation can be regulated through an antitumor immune response^{2,5}



QUESTION 3. How do we know that some tumors may evade the immune system?

Some cancer cells can reinvent themselves through a number of mechanisms that may allow them to evade the immune response. For instance, tumor cells may make themselves harder to detect by decreasing the expression of certain tumor-specific antigens.⁵ Cancer cells can also produce a local state of immune suppression within the tumor microenvironment.⁹ It appears that they may do this by secreting immunosuppressive cytokines,^{5,9} recruiting immunosuppressive cells such as T_{reg} cells,¹⁰ and exploiting inhibitory immune pathways known as immune checkpoints.⁵

Immune checkpoints are stimulatory and inhibitory signals that regulate the duration and level of the immune response. The inhibitory immune checkpoints act like brakes on the immune response. The normal role of immune checkpoints is to minimize collateral tissue damage and limit autoimmunity, which could occur if the immune response was not under tight control. Some tumor cells appear to exploit some of these inhibitory immune checkpoints, resulting in the inactivation of T cells.⁵

Various immune checkpoints that appear to regulate T-cell activity have been identified, and include cytotoxic T-lymphocyte antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1), and lymphocyte activation gene 3 (LAG-3).⁵ These checkpoints may function at different phases in the immune response to regulate the duration and level of T-cell activity.⁵

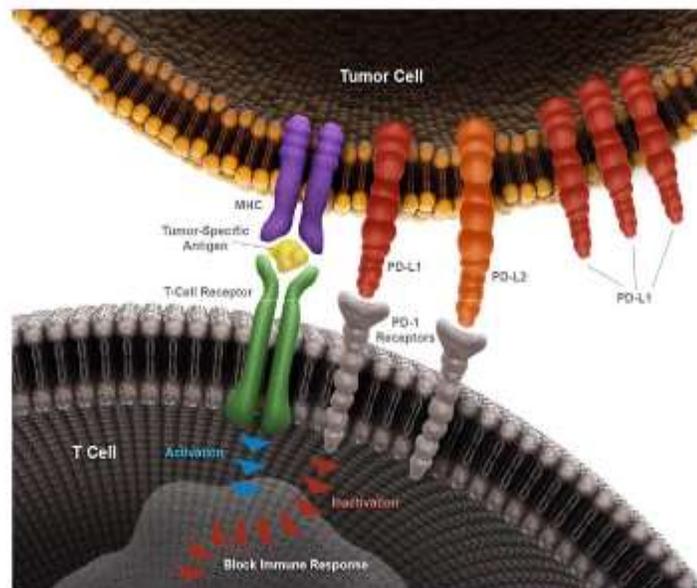
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QUESTION 4. Are there any salient research trends emerging from investigations of all of the complex mechanisms used by tumors to evade the immune system?

It is becoming evident that exploiting inhibitory immune checkpoints is one mechanism tumor cells may use to evade the immune system. Emerging research has identified PD-1 as one of the immune checkpoints that tumor cells may exploit. The PD-1 immune checkpoint is expressed on activated T cells during the effector phase of T-cell activity. Activation of the PD-1 checkpoint may downregulate T-cell activity within the tumor microenvironment.⁵

The PD-1 immune checkpoint pathway comprises the PD-1 receptor and its dual ligands PD-L1 and PD-L2. Some tumor cells may evade the immune response by expressing these dual ligands for PD-1. Engagement of the PD-1 receptor by one of its ligands may inhibit T-cell activity in the tumor microenvironment (Figure 2).⁵

Figure 2. Engagement of the PD-1 receptor by its ligands PD-L1 and PD-L2 may downregulate T-cell activity in the tumor microenvironment⁵



PD-L1 may be overexpressed by some tumor cells.¹¹ The significance of PD-L1 expression in cancer remains a focus of oncology research.

In conclusion, a patient's own immune response may be a powerful ally in the fight against cancer. Future studies will be instrumental in elucidating the role of immune-response regulators such as immune checkpoints in cancer.