Understanding Metastatic Melanoma and Immuno-Oncology Approaches

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Introduction to Immuno-Oncology (I-O)

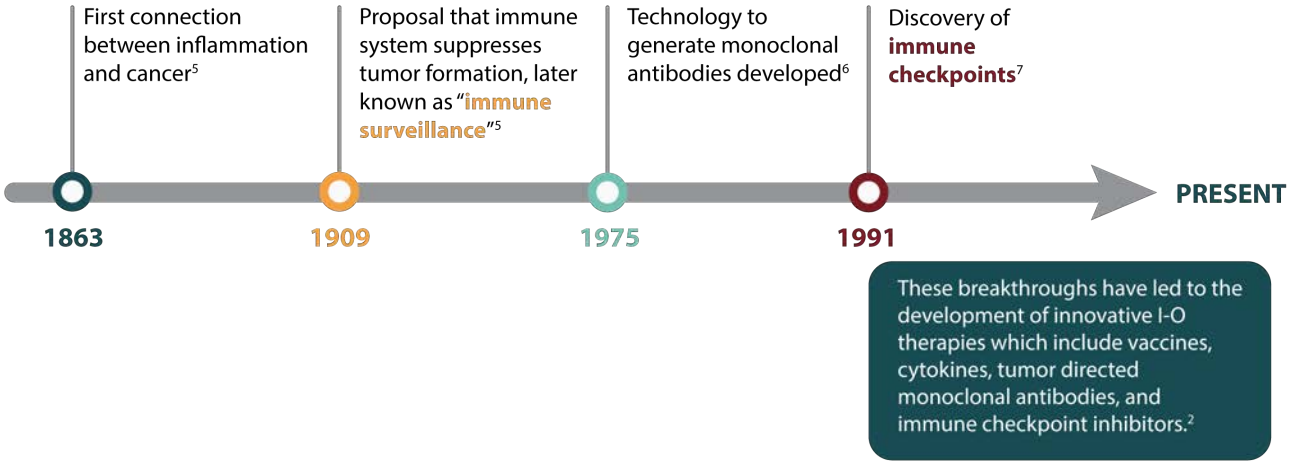
What's I-O?

Immuno-oncology is an area of cancer research that utilizes the body's own immune system to fight diseases.[1-3]

I-O has progressed considerably in the last 30 years with development of many I-O therapies including vaccines, cytokines, tumor-directed monoclonal antibodies, and immune checkpoint inhibitors.[2,4]

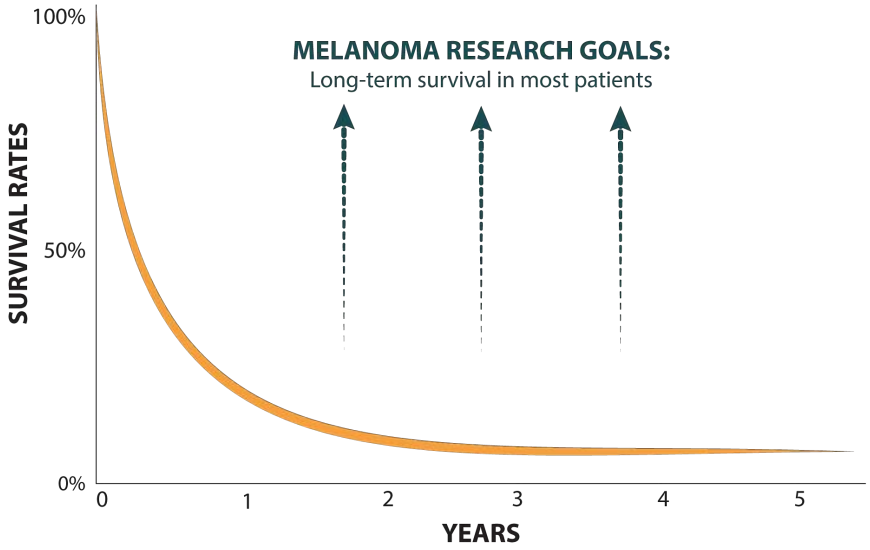
History of I-O

In 1909, the proposal was made that the immune system does play a role in suppressing tumor formation. This is now known as **immune surveillance**. There have been further advancements in the field of immuno-oncology throughout the century as detailed below.[5-7]



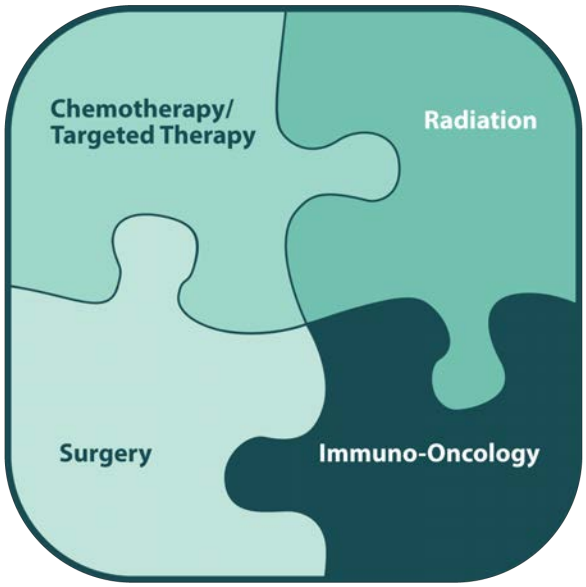
Treatment modalities in metastatic melanoma

The estimated 1- and 5-year survival for patients with metastatic melanoma remains low at 25% and 16%, respectively. Delivering a long-term survival benefit to the majority of patients with advanced melanoma remains a goal.[8-9]



Metastatic melanoma survival rates[8-9]

Traditionally, the options available for all cancers were chemotherapy, targeted therapy, radiation, and surgery, which are all intended to target the tumor.[1-2] The **emerging modality of immuno-oncology** is one potential method to improve outcomes for people with metastatic melanoma. Immuno-oncology is different because it seeks to use the **patient's own immune system to fight the tumor**.



Immuno-oncology is an emerging treatment modality for metastatic melanoma[1]

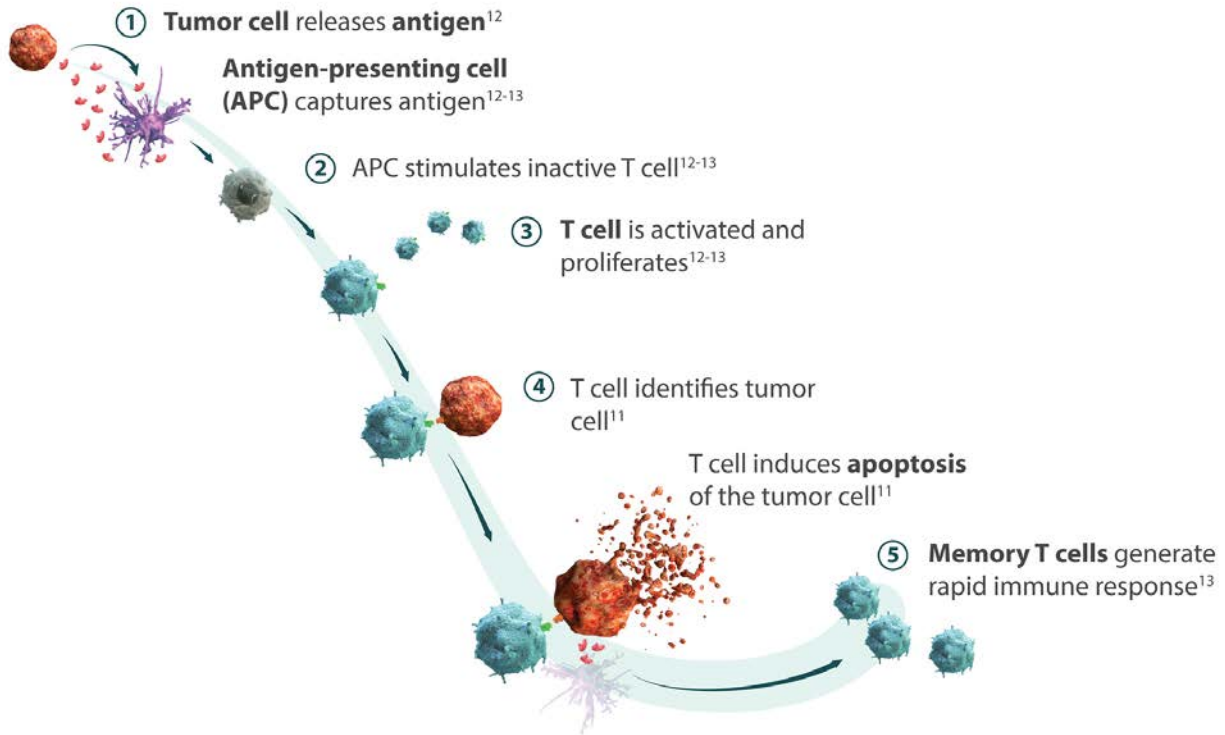
Role of the immune system in melanoma

The immune system has natural anti-tumor activity

The immune system recognizes tumors and initiates an anti-tumor response to eliminate cancer. This is also known as tumor immune surveillance.[10] Melanoma cells express **unique antigens** such as Tyrosinase, gp100, or MART-1/Melan-A, which have been associated with T-cell recognition and the immune response. These tumor antigens signal the immune system's T cells to attack the melanoma.[11]

Steps in the normal immune system response to melanoma:

1. Tumors express and release **tumor-associated antigens**; **antigen-presenting cells (APCs)** capture and process these antigens and present them to T cells.[12]
2. The process of an APC recognizing a specific antigen produced by the tumor and presenting it to the T cell is the **first stimulatory signal** involved in **T-cell activation**. Then a **second co-stimulatory signal** from the APC completes T-cell activation.[12-13]
3. T cells are then able to **proliferate** and **travel** throughout the body. T cells proliferate by cloning themselves, creating more activated T cells that are able to recognize a specific melanoma antigen.[12-13]
4. Once T cells are activated, **cytotoxic T cells** migrate to the melanoma, where they can **recognize** expressed tumor antigen and **destroy** melanoma cells by releasing apoptosis inducing proteins such as granzymes and perforins.[11]
5. A subset of activated T cells becomes **memory T cells** to help generate a rapid cell-mediated immune response in the future.[13]



Pathway showing normal anti-tumor activity of the immune system[11-13]

Melanoma can produce a strong immune response

Melanoma is one of the most immunogenic cancers, which makes it a prime candidate for research into I-O.[10,14]

- There have been cases of spontaneous regression in the primary melanoma tumor. In other words, it did not regress as a result of treatment, but as a result of the body's own immune system.[14]
- Histopathologists have found evidence of lymphocytes infiltrating melanoma tumor cells, including T cells which exhibit cytotoxic effects. In addition, melanoma-specific T cells have also been found in the peripheral blood of melanoma patients.[14]

Tumor evasion of the immune system

Mechanisms of tumor evasion

Melanoma tumors can adapt to the body's immune system, which can lead to evasion of immune destruction and tumor growth. This ability to evade immune destruction is an emerging hallmark of cancer.[10,15] There are many mechanisms that may explain how tumors accomplish immune system evasion:

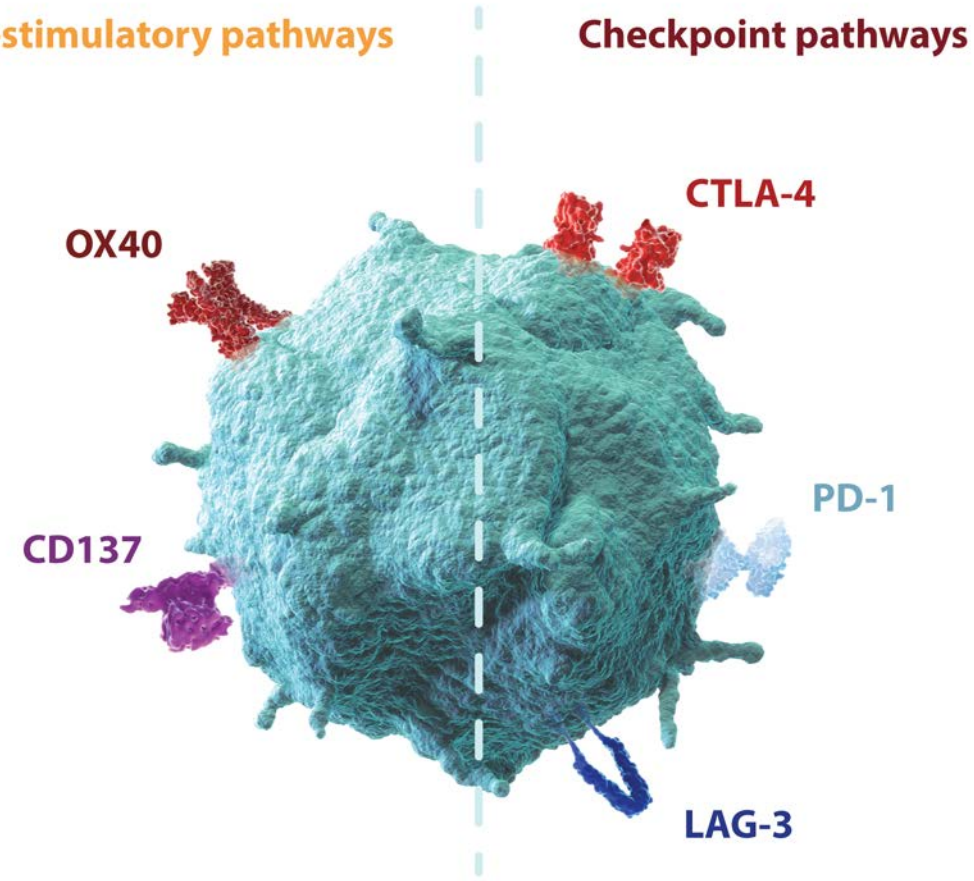
- **Tumor antigens** – Escaped tumors can downregulate the expression of their antigens. This allows tumors to be no longer recognized by cytotoxic T cells.[10,14] Similarly, tumors can lose expression of antigens on the cell surface, such as HLA, that are necessary to show them as targets for the immune system.[10]
- **Immune-suppressive cytokines** – Tumors can secrete immune-suppressive cytokines that may interfere with the function of the immune response to the cancer. This can occur by tumors attracting suppressive immune cells, such as regulatory T cells and myeloid-derived suppressor cells, that can dampen immune response.[10]
- **Physical barrier** – Sometimes, cancer cells exist in a harsh environment composed of a thick fibrous stroma, a physical barrier to immune cells that prevents them from getting in and recognizing the cancer cells.[3]
- **Immune activation and inhibition pathways** – Tumors may dysregulate molecules in activation and inhibition pathways of the immune system to disable the anti-tumor response. For example, tumors can express molecules, such as PD-1 ligands, that decrease T-cell proliferation and activation at the tumor site.[10] **This is an area of much research in I-O.**

Immune system co-stimulatory and checkpoint pathways

Tumors can exploit specific molecular interactions to inactivate T cells

Dysregulation of molecules that enhance or inhibit T-cell function may result in the reduction of the immune system's ability to eradicate melanoma cells. This specific tumor immunoevasive mechanism via exploiting immune activation and inhibition pathways is an area of much research.[2,11]

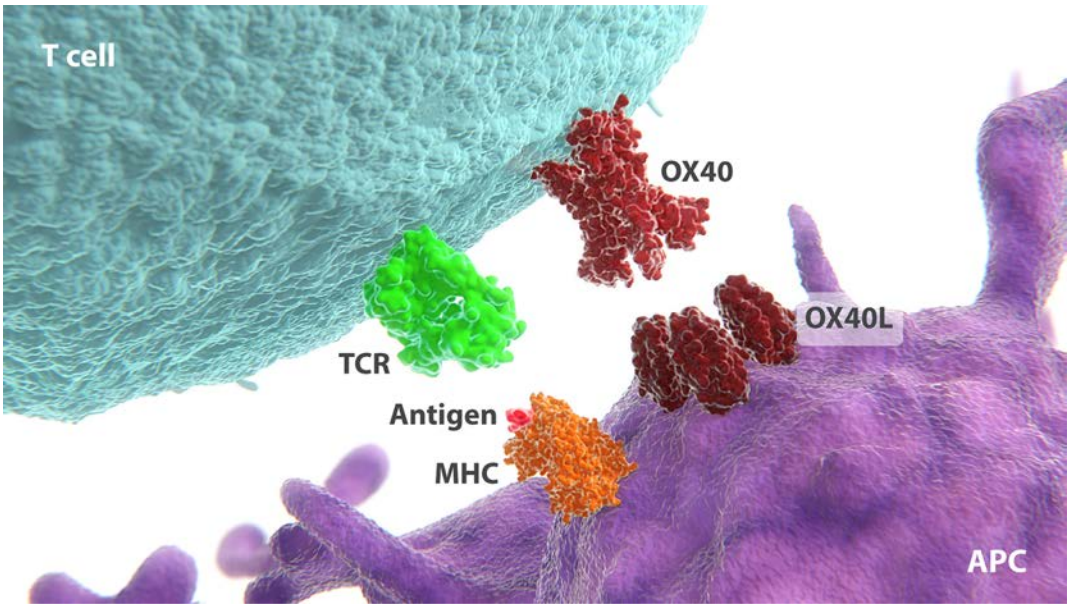
There are many distinct immune pathways that play a role in T-cell modulation in different phases of T-cell response. OX40 and CD137 co-stimulate the immune response.[16] These are counterbalanced by immune checkpoint pathways such as CTLA-4, LAG-3, and PD-1, which inhibit the immune response.[11,17-19]



Tumors have evolved mechanisms to inactivate T cells by exploiting co-stimulatory (e.g., OX40 and CD137) and immune checkpoint (CTLA-4, PD-1, and LAG-3) pathways[11,16,17-19]

Co-stimulatory pathways

There are a number of different co-stimulatory pathways including members of the tumor necrosis factor receptor family, such as **OX40** and **CD137**. T cells express the OX40 and CD137 receptors and bind to their respective ligands, OX40 ligand and CD137 ligand, on APCs to deliver co-stimulatory signals which enhance T-cell activity. Once activated, T cells proliferate, migrate, and attack melanoma cells.[20] Research is ongoing into strategies that augment the OX40 and CD137 co-stimulatory pathways in order to boost anti-tumor immunity in melanomas.



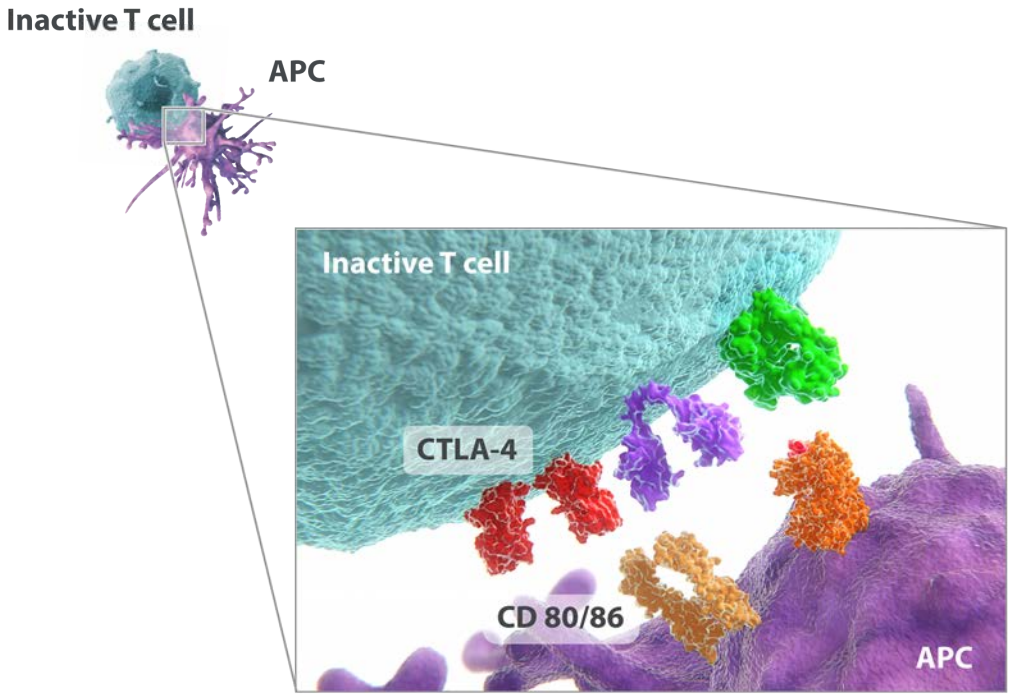
Two stimulatory signals are needed to complete T-cell activation:
1) T-cell receptor (TCR) recognition of the tumor antigen on the APC, and
2) Binding of a co-stimulatory receptor (e.g., OX40 or CD137) to its ligand[20]

Checkpoint pathways

In a healthy individual, immune checkpoint pathways maintain immune homeostasis. It creates checks and balances in the immune system in order to prevent T-cell activation past a certain threshold that may cause harm to the host if exceeded. There are several kinds of these checkpoint pathways, including **CTLA-4**, **LAG-3**, and **PD-1**. These exist naturally and are up-regulated in activated T cells to mediate responses and prevent them from attacking healthy tissues.[11]

CTLA-4 is expressed on activated T cells. If left unchecked, activated T cells may react with and damage normal tissue. To limit this damage, T-cell activity is kept in check by the expression of the immune checkpoint molecule CTLA-4 on the surface of T cells. This limits the priming phase of T-cell responses within the lymph nodes. CD80/86 on the antigen-presenting cell is the ligand for CTLA-4. Binding of this receptor-ligand pair downregulates T-cell activity.[11]

- Tumors, such as melanoma, may exploit the CTLA-4 pathway to weaken the immune response by decreasing T-cell activity, migration, and elimination of tumor cells.[11]



Interaction between the T-cell receptor CTLA-4 with its ligand CD80/86 on the APC downregulates T-cell activity[11]

Expression of LAG-3 upon T-cell activation helps support feedback inhibition, similar to CTLA-4. The main ligand for LAG-3 is MHC class II molecules on APCs. Though its role is not completely understood, studies have shown that LAG-3 is associated with T-cell exhaustion (T cells with poor immune effector function).[11,21]

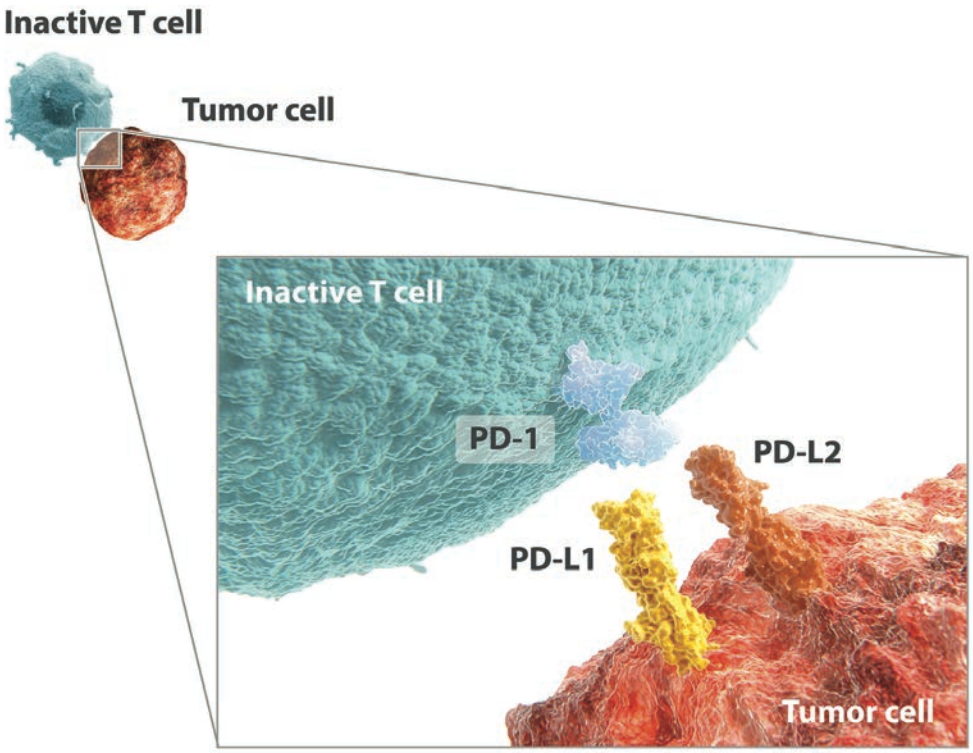
- Tumors, such as melanoma, may exploit this pathway to attenuate the ability of the immune system to detect and destroy them.[11,21]

PD-1 is another checkpoint molecule expressed on activated T cells that aids in the negative regulation of T-cell effector activity.

- Tumors, such as melanoma, express the PD-1 ligands, PD-L1 and PD-L2, to turn down the immune response.[22]

  Interaction of PD-1 on effector T cells with ligands PD-L1 and PD- L2 on melanoma cells primarily plays a role in the effector phase of a T-cell response in the tumor microenvironment.[11]

  Binding of PD-1 to PD-L1 or PD-L2 negatively regulates the effector phase of the immune response in peripheral tissue. PD-L1 and PD-L2 can bind to the PD-1 receptor on T cells to inhibit T-cell activity and suppress the T-cell attack directly at the tumor site. By exploiting the PD-1 checkpoint pathway, cancer cells evade the immune response and continue to proliferate.[11,12,15,23]



PD-L1 and PD-L2 on melanoma cells can bind to the PD receptor on T cells to inhibit T-cell activity and suppress the T-cell attack directly at the tumor site[11,12,15,23]

The immune checkpoint molecules, CTLA-4, LAG-3, and PD-1, are necessary for immune homeostasis.[11] However, **tumors are able to exploit these immune checkpoint pathways and suppress the immune system, which ultimately leads to tumor growth**.[11] Ongoing research seeks to understand if blocking the CTLA-4, LAG-3, and PD-1 pathways may augment T-cell activation and subsequent migration and attack of tumor cells.

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