Transcript - A Closer Look at Mechanism of Pathways in Melanoma with Dr. Jedd Wolchok

Advanced melanoma is an aggressive disease that carries a deep emotional burden for patients and their families.

(And) that's why I'm here today, to share the advancements in our understanding of the immune pathways involved in melanoma.

With this knowledge, we hope to one day change melanoma from a disease that patients are dying from, to a disease that patients can live with or without.

My name is Dr. Jedd Wolchok and I am the Lloyd J. Old/Virginia and Ludwig Chair in Clinical Investigation, and Chief of the Melanoma and Immunotherapeutics Service at Memorial Sloan-Kettering Cancer Center.

My research and clinical focus is in the care of melanoma patients, and specifically, with immuno-oncology approaches.

As oncologists, we have spent decades figuring out ways to treat the melanoma tumor itself, with traditional therapies such as chemotherapy and targeted therapy, radiation, and surgery.

(And) these have benefited some patients. For many years, survival with traditional therapies was quite low.

However, better options are needed that provide long- term survival for more patients.

Delivering a long-term survival benefit to most patients with advanced melanoma remains a goal.

What excites me is the ongoing research that involves harnessing the potential of the patient's own immune system to treat the cancer, which differs from treating the cancer itself. It is a modality known as immuno-oncology.

What's unique about the immune system is that it can remember what it has experienced by maintaining a memory of previous encounters with antigens.

Let's take a deeper dive into how this may work.

We all know that the immune system plays a vital role in defending against infectious pathogens, and it normally does a very good job of that.

The success of childhood vaccination is a testament to that.

(Now) based upon the important role that the immune system plays in defending against dangers it is not surprising that the immune system plays a role in defending against non–pathogen-derived sources of danger such as melanoma.

In a normal state, the immune system recognizes tumor cells and can mount an active and highly adaptable antitumor immune response through tumor immune surveillance — which is the ability of the immune system to seek and destroy melanoma cells. Typically melanomas present tumor specific antigens.

Circulating antigen-presenting cells collect these tumor antigens and present them to T cells in order to activate them. Activated T cells then proliferate and travel throughout the body, and once they encounter a melanoma cell, they release apoptosis-inducing proteins, such as granzymes and perforins which results in tumor destruction.

The problem is that in melanoma, cancer cells may be able to hide from the immune system.

How is that? Well, through various mechanisms that evade and suppress the immune system.

One mechanism of evasion is due to a lack of recognition by immune cells. The immune system is designed to destroy bacteria and viruses, which it sees as foreign.(But) it is trained to ignore or tolerate normal tissue.

If not, we'd end up with an immune response against normal, healthy cells.

Cancerous melanoma cells can mimic normal cells so that the immune system is less likely to recognize and destroy them.

That's not all: Researchers have learned some of the mechanisms underlying immune suppression and have identified several ways in which cancers can hide themselves from the immune system.

The cancer can secrete immune-suppressive cytokines that may interfere with the function of the immune response to the cancer.

Cancers can also attract suppressive immune cells, such as regulatory T cells and myeloid-derived suppressor cells.(And) these may dampen the immune response. Cancers may lose expression of antigens on the cell surface, such as HLA, that are necessary to show them as targets for the immune system. Sometimes cancer cells exist in a very harsh environment composed of a thick, fibrostroma.

This is a physical barrier to immune cells that prevents them from getting in and recognizing the cancer cells.

A tumor immunoevasive mechanism that is very high on everyone's radar at the moment is the dysregulation of molecules that enhance or inhibit T-cell function that may result in the reduction of their ability to eradicate melanoma cells.

Tumors have figured out ways to inactivate T cells by exploiting co-stimulatory and immune checkpoint pathways. These pathways are known mechanisms by which tumor cells are able to evade detection and destruction by the immune system.

Each is a distinct immune pathway that plays a role in T- cell modulation in different phases of T-cell response.

Some pathways, such as OX40 and CD137 co-stimulate the immune response. These are counterbalanced by immune checkpoint pathways such as CTLA-4, LAG3 and PD-1, which inhibit the immune response.

Let's take a look at how these pathways regulate T cell responses. The first stimulatory signal needed for T cells to destroy melanoma cells is an interaction that allows T cells to recognize the target.

That's the T-cell receptor recognizing the tumor antigen being presented by the antigen presenting cell. Then a co-stimulatory signal is transduced by the binding of a receptor on the T cell to its ligand on the antigen presenting cell. This completes T-cell activation.

There are a number of 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, OX40L and CD137L on antigen presenting cells to deliver co-stimulatory signals which enhance T cell activity.

Once activated, T cells proliferate, migrate, and attack melanoma cells. Research is ongoing into strategies that augment the OX40 and CD137 co-stimulatory pathways in order to boost anti-tumor immunity in melanomas.

In a healthy individual, stimulation of T cell responses that we just discussed is not left unchecked

Normally, immune checkpoint pathways maintain immune homeostasis or checks and balances in the immune system.(And) they say to the T cell, once you get activated, be careful.

Don't go past a certain threshold, or else there can be further problems. There are a number of such checkpoint pathways including CTLA-4, LAG3 and PD1.

These exist naturally and are up-regulated in activated T cells to mediate responses and prevent them from attacking healthy tissues.

So how does this work?

Let's start by taking a look at the CTLA-4 pathway. CTLA-4 is expressed on activated T cells. 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 down- regulates T-cell activity.

Melanoma tumors may exploit the CTLA-4 pathway to weaken the immune response by decreasing T-cell activity, migration, and elimination of tumor cells.

Like CTLA-4 the immune checkpoint molecule LAG3 is also expressed on T cells and other cells of the immune system.

Expression of LAG3 upon T cell activation is in keeping with its role in feedback inhibition, similar to CTLA-4.

The main ligand for LAG3 is MHC class II molecules on antigen presenting cells.

Though its role is not completely understood, studies have shown that LAG3 is associated with T cell exhaustion. That is, T cells with poor immune effector function.

As with CTLA-4, melanoma cells may exploit this pathway to attenuate the ability of the immune system to detect and destroy them. Now let's look at PD-1, another immune checkpoint molecule.

Remember, melanomas present tumor specific antigens. Antigen-presenting cells collect these tumor antigens and present them to T cells. Once activated, T cells proliferate, migrate, and attack the tumor. They recognize the tumor by the antigens presented.

However, melanoma tumors express the PD-1 ligands, PD-L1 and PD-L2.

Interaction of PD-1 on effector T cells with 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.

Binding of PD-1 to PD-L1 or PD-L2 negatively regulates the effector phase of the immune response in peripheral tissue.

In other words, 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.

As you can see the immune checkpoint molecules, CTLA- 4, LAG3 and PD-1, are also necessary for immune homeostasis.

Tumors are able to exploit these immune checkpoint pathways and suppress the immune system. Ongoing research seeks to understand if blocking the CTLA-4, LAG3 and PD1 pathways may augment T-cell activation and subsequent migration and attack of tumor cells.

If the immune system is supported in its fight to overcome the tumor's defense mechanisms, the potential to outsmart cancer may be realized.

Immuno-oncology research will continue to inform future strategies, including new pathways and rationale for immunotherapy combinations and sequences such as immunotherapy with chemotherapy or targeted therapies, surgery, radiation or other immunotherapies.

Thanks to many years of research, we have now identified a family of co-stimulators and immune checkpoint molecules that modulate T-cell activation and proliferation.(And) it is my hope that by continuing to learn about immuno-oncology, more stories can be told of patients no longer dying from the disease but living with or even without melanoma.

Thank you.