Transcript - Mechanism of Pathways in Multiple Myeloma

[ANDERSON]

The scientific understanding of multiple myeloma has significantly advanced over the past few decades.

This is largely because of a greater understanding of the numerous signaling cascades that drive this malignant cell growth and survival associated with this largely incurable and fatal disease.

Advances in the understanding of cellular and molecular immunology have led to strategies that utilize the immune system to help fight cancer.

This approach, focused on the potential to harness the body's own immune response to help fight cancer, including multiple myeloma, is called immuno- oncology.

That is what has inspired us to come and talk to you today.

My name is Dr. Ken Anderson and I am the director of the Jerome Lipper Multiple Myeloma Center at the Dana-Farber Cancer Institute and the Kraft Family Professor of Medicine at Harvard Medical School.

[LONIAL]

And I'm Dr. Sagar Lonial. I am professor and Vice Chair of Clinical Affairs in the Department of Hematology and Medical Oncology at Emory University School of Medicine.

In the preceding video, Immuno-Oncology in Multiple Myeloma, we spoke about unmet needs in multiple myeloma.

Despite recent advances, multiple myeloma remains a largely incurable disease, with fewer than half of the patients surviving 5 years after diagnosis.

Additional strategies intended to reduce tumor burden and suppress residual disease are still needed for the majority of multiple myeloma patients.

We also talked about immune surveillance and briefly discussed the mechanisms that cancer cells adopt to evade that surveillance.

This is a concept referred to as immune evasion.

Research has helped us to better understand the mechanisms involved focusing on the interactions between the immune system and cancer cells. And this is beginning to uncover potential new pathways that work with the immune system to attack malignant cells.

[ANDERSON]

To get a better understanding of these pathways implicated in multiple myeloma and why they are subject to such extensive research, it may be helpful to start by reviewing the cancer immunity cycle.

Basically, tumor cells are eliminated by the immune system via a self-propagating cyclical process also known as the cancer-immunity cycle.

This cycle can be divided into 7 major steps.

It starts with antigen release by cancer cells and ends with cancer cell death.

The cycle is characterized by the accumulation of immune-stimulatory factors that promote deep immune cell responses.

But it is also characterized by the expression of inhibitory factors that prevent or limit the immune response through feedback mechanisms.

Negative feedback mechanisms are in place to keep the cycle in check and prevent overstimulation of the immune response.

Without this mechanism, autoimmunity can become a problem if the immune system starts to attack normal cells.

[LONIAL]

So Ken, it is not surprising that in cancer patients, dysregulation at various points in the cancer immunity cycle can facilitate immune evasion and allow cancer cells to grow.

For example, tumor antigens may not be detected.

Or perhaps T cells are unable to hone in on, or infiltrate tumors.

Or the tumor microenvironment may suppress effector cell function.

The point is, these are just a few examples, but they are all rich areas for exploring how to help harness the immune system to attack myeloma cells.

[ANDERSON]

A hallmark of patients with multiple myeloma is suppression of the endogenous immune response, both humoral and cellular.

Let's take a look at some of the examples of processes which, when dysregulated, may result in immune dysfunction. Sagar?

[LONIAL]

In healthy bone marrow, hematopoietic stem cells are able to differentiate into blood cells including T cells and Natural Killer cells as well as plasma cells, which produce immunoglobulins that are able to elicit an immune response.

However in multiple myeloma, malignant cells proliferate uncontrollably and impair normal blood-forming and plasma cells in the bone marrow, resulting in the inability to mount an immune response.

Myeloma cells also overproduce a defective, monoclonal immunoglobulin, M protein, which has limited antigen reactivity.

As a result, in multiple myeloma there may be deficits in antigen presentation leading to a less robust immune response.

[ANDERSON]

Myeloma cell growth may also be associated with an imbalance in the natural feedback mechanisms that modulate the immune response. Myeloma cells may cause down-regulation of co-stimulatory receptors, which dampen the immune response.

Or they may exploit or up-regulate expression of immune checkpoints, or inhibitory signaling pathways, which facilitate immune suppression.

[LONIAL]

Investigating these pathways may lead to a better understanding of how immune evasion may be overcome.

[ANDERSON]

There is a number of interesting strategies being investigated to modulate the immune system in patients with multiple myeloma.

Sagar, would you like to get this started?

[LONIAL]

Sure.

Current research in immunotherapy strategies includes vaccinating patients against tumor-associated antigens, enhancing immune cell function, or modulating immune activity.

Let's start with vaccines.

Vaccines trigger an immune response, facilitating B- and T-cell recognition.

Accessory cell–based vaccines and protein–secreting vaccines are currently being investigated in the treatment of multiple myeloma.

Cytokines are messenger molecules that help control the growth and activity of cells of the immune system.

A number of antibodies that block or stimulate cytokine pathways are also under investigation.

Adoptive T-cell transfer is another interesting strategy.

It involves the removal of T cells from the patient, genetic modification or chemical treatment of the T cells to enhance activity, and finally reintroduction of the modified T cells into the patient.

The use of T cells engineered to express chimeric antigen receptors or antigens expressed by myeloma cells is being investigated.

Ken, would you like to talk about other areas of interest?

[ANDERSON]

I'd be happy to.

Currently, another area of research is largely focused on activity within the tumor microenvironment.

Targeted therapies such as tumor-directed antibodies directly interact with antigens on tumor cells.

Upon binding, several processes can be triggered.

First, tumor cells are essentially marked for destruction via antibody-dependent cellular cytotoxicity, also known as ADCC. Complement proteins coming towards myeloma cells tagged by an antibody bound to antigen → cell death

Second, the antibody-antigen interaction can activate a cascade of proteolytic enzymes that destroy the cell.

This is known as complement-dependent cytotoxicity or CDC.

Antibody binds to antigen on myeloma cell → cell death

Finally, antibody recognition of cell-surface antigens on the tumor cell can trigger apoptotic or death pathways in the tumor.

It may also neutralize growth survival pathways.

Several of these antigen targets and pathways are under investigation for multiple myeloma.

[LONIAL]

A fundamentally, different approach I find particularly exciting is research in the field of immuno-oncology.

Immuno-oncology is based on the premise that the immune system is the body's natural tool for recognizing and fighting disease.

Unlike traditional approaches such as those I have previously discussed that target the tumor, immuno-oncology focuses on empowering the intrinsic capabilities of the immune system.

Let's take a deeper look at how leveraging these capabilities can help fight cancer.

Immune effector cells, such as activated T cells, B cells, and Natural Killer Cells, have cell surface receptors which, when bound to their respective ligands, transmit activating or inhibitory signals for growth, proliferation, and even cytotoxicity.

Antibodies may recognize these receptors and act as agonists or antagonists. It is thought that these interactions may modify the immunosuppressive effects exerted on immune cells by the tumor and its microenvironment.

Myeloma cells can cause increased expression of inhibitory receptors on immune cells in order to evade recognition and cytotoxic effects.

Researchers are exploring the potential of how modulating ligand-receptor interactions may influence cytotoxicity against myeloma cells.

[ANDERSON]

Additionally, there are receptors on immune cells that increase proliferation and cytokine production, when they are activated.

Ongoing research is helping us understand how modulating these pathways may theoretically enhance the ability of immune cells to induce myeloma cell death.

Several of these pathways are being investigated, including B7, CD137, KIR, PD-1, and SLAMF7.

As you can tell, this field represents a new way of looking at how myeloma cells interact with their environment and how we in turn can use that knowledge to further our research.

[LONIAL]

It is my hope that ongoing research will lead to a better understanding of how signaling pathways are mediated and how immuno-oncology strategies may influence these pathways.

[ANDERSON]

This is quite exciting because modulating the interactions between myeloma cells and the bone marrow microenvironment by harnessing the patient's own immune system is a fundamentally different approach under investigation for multiple myeloma.

We hope that you've enjoyed this series and found it informative.

Thank you for joining us.