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Commentary

Immunotherapy Resistance: The Immunotherapy Puzzle Solving the Resistance Conundrum

Thornhill Goes*

Department of Immunology, University of Split, Split, Croatia

ABOUT TO STUDY

Immunotherapy has innovated cancer treatment, offering hope to countless patients who once had few options. By controlling the body's own immune system to fight cancer, immunotherapy has been a game-changer, particularly for cancers that were once considered difficult to treat, like melanoma, lung cancer, and certain blood cancers. However, despite the successes, there remains a significant problem: Immunotherapy resistance. For some patients, the initial success of immunotherapy is followed by a relapse, where the cancer becomes resistant to treatment. Understanding why this happens has long been a scientific "cold case" a mystery that researchers have struggled to crack. In recent years, however, new breakthroughs have begun to shed light on this elusive problem.

Immunotherapy and its successes

Immunotherapy, particularly the use of immune checkpoint inhibitors, has transformed oncology in recent decades. Immune checkpoint inhibitors like pembrolizumab (Keytruda) and nivolumab (Opdivo) block the "brakes" that cancer cells put on immune system responses, allowing T cells to more effectively attack cancer cells. These therapies have shown remarkable success, especially in cancers such as melanoma, non-small cell lung cancer, and bladder cancer, where they can provide long-term remission and in some cases even cure. However, not all patients experience these benefits, and many eventually develop resistance to treatment.

In fact, resistance to immunotherapy has emerged as one of the most vexing challenges in cancer treatment. While some tumors shrink significantly after immunotherapy, others appear to adapt, rendering the therapy ineffective. Understanding why this happens has been a major focus of cancer research, as overcoming this resistance could unlock new possibilities for treatment and save many lives.

The mystery of resistance

The concept of immunotherapy resistance is somewhat counterintuitive. If the immune system is capable of recognizing and destroying cancer cells, why does it sometimes fail? The answer lies in the complex interactions between cancer cells and the immune system. Tumors are not isolated islands; they exist within a rich environment known as the Tumor Microenvironment (TME), which includes immune cells, blood vessels, signaling molecules, and other components. The TME is a dynamic and hostile place for immune cells, and over time, cancer cells evolve to survive and thrive within it.

One of the key mechanisms by which tumors resist immunotherapy is by altering the immune cells in the TME. Cancer cells can recruit immune cells that suppress the immune response, such as Myeloid-Derived Suppressor Cells (MDSCs) or regulatory T cells (Tregs). These cells create an immunosuppressive environment that prevents the immune system from attacking the tumor. Additionally, tumor cells may upregulate certain proteins, such as PD-L1, which act like "brakes" on T cells, preventing them from recognizing and killing cancer cells.

Another factor contributing to resistance is tumor heterogeneity — the vast genetic and molecular diversity found within tumors. Different parts of the same tumor can have different mutations, some of which may make them more resistant to immune detection or immune cell attacks. Tumors with certain mutations, particularly those in genes that regulate immune responses, may become "invisible" to the immune system, making immunotherapy less effective.

Overcoming resistance

Cracking the "cold case" of immunotherapy resistance holds immense promise for improving cancer treatment. By understanding the specific mechanisms that cause resistance, researchers are beginning to develop strategies to counteract them. For instance, new drugs that target immune checkpoint proteins, such as TIM-3 inhibitors, are being tested to enhance the immune response in resistant tumors. Other approaches

Correspondence to: Thornhill Goes, Department of Immunology, University of Split, Split, Croatia; E-mail: goest@gmail.com

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focus on "reinvigorating" exhausted T cells, restoring their ability to attack cancer cells.

Moreover, combination therapies that use immunotherapy alongside traditional cancer treatments, such as chemotherapy or radiation, are showing promise. These therapies may help break down the tumor's defenses, allowing immunotherapy to be more effective.

CONCLUSION

The mystery of immunotherapy resistance is one of the most complex challenges in modern oncology. While some cancers initially respond well to immunotherapy, others evolve ways to evade or suppress immune attacks, leading to treatment failure. However, recent breakthroughs in understanding the tumor microenvironment, immune checkpoints, and immune cell behavior are providing important insights into why this happens. With these new discoveries, researchers are developing innovative strategies to overcome resistance, offering hope for more effective treatments and better outcomes for cancer patients. As we continue to crack the cold case of immunotherapy resistance, the future of cancer treatment looks brighter than ever.