How Does the Immune System Fight Cancer?

The immune system has a natural ability to shut down cells that grow out of control, but cancer has many ways to get around these defenses. Here's a look at the different players in the immune response and how immunotherapy can help them do a better job.

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The immune system is an amazing accomplishment of evolution. Day in and day out, an army of immune cells patrols the body, looking for invaders like bacteria and viruses as well as distressed cells, such as cancer cells growing out of control.

If things are working right, sentinel cells recognize pathogens and abnormal cells and call other soldiers into action to destroy them. Many things can go awry with such a complex system, however, and cancer has developed numerous ways to hide from or disable immune responses.

But researchers have in turn devised ways to restore the immune response against cancer. These include immunotherapy drugs that take the brakes off T cells and adoptive cell therapies that use natural or genetically engineered T cells. New therapies that employ macrophages and natural killer (NK) cells are in the works. Current immunotherapy doesn't work equally well for all patients or for all types of cancer, but experts are optimistic.

"The human immune system is so incredibly powerful that we think it can be leveraged against multiple targets," says Marcela Maus, MD, PhD, of the Massachusetts General Hospital Cancer Center.

An Immune System Primer

It has long been clear that the immune system can naturally fight cancer. Mice without a functional immune system and people with compromised immunity are prone to developing malignancies. Many early-stage cancers never progress, and some even go into remission on their own. But, says Nicholas Jarjour, PhD, a Damon Runyon postdoctoral fellow at the University of Minnesota Medical School, "There's not a lot known about those normal processes of fighting cancer."

The immune response is carried out by a diverse array of white blood cells produced in the bone marrow (see "Cells of the Immune System," below). They patrol the body looking for pathogens and damaged cells, a process known as immune surveillance. This is straightforward for bacteria

and viruses, which are recognized as “foreign.” Fighting cancer is trickier because malignant cells are derived from normal cells. During their development, immune cells that target the body’s own proteins are eliminated so they won’t cause autoimmunity.

The two main branches of immunity are the innate and adaptive immune systems. When a threat is encountered, the innate, or nonspecific, immune system goes into action first, providing built-in protection. Neutrophils and other first responders mount a rapid response against bacteria, parasites and allergens.

Macrophages, or “big eaters,” vacuum up pathogens, cellular debris and other harmful substances. Natural killer cells recognize and destroy virus-infected and malignant cells. These immune cells also release cytokines, chemical messengers that promote inflammation and call other fighters into action. Sentinels known as antigen-presenting cells (APCs) display proteins from pathogens (antigens) or abnormal tumor proteins (neoantigens) to alert B cells and T cells.

“Basically, the immune system is dependent on noticing something that’s different from the normal state of the body,” says Jarjour. “Often, in the case of a tumor, there’s a mutated protein or something else that the immune system can specifically recognize. If it can identify something that’s seemingly foreign, it can use that as a basis to mount an immune response that will destroy the tumor.”

APCs, such as macrophages and dendritic cells, are the main link between the innate immune system and the adaptive immune system, which responds to specific threats. B cells and T cells are more specialized, each recognizing a single antigen. Some APCs carry antigens to lymph nodes, where T cells learn to identify them.

B cells evolve into plasma cells, which produce antibodies that bind to foreign antigens like a lock and key. B cells don’t seem to play much of a role in fighting cancer.

T cells are a different story. CD4 “helper” T cells are like generals that coordinate the immune response. CD8 “killer” T cells are like soldiers that destroy cells infected with viruses or malignant cells. Another subset known as regulatory T cells turn off immune responses to prevent harm to the body.

What’s more, the immune system has a memory. When an immune response has run its course, a set of long-lived memory B cells and T cells remain, enabling the immune system to respond more efficiently to the same threat in the future.

Hot and Cold Tumors

But cancer has several tricks for evading immune defenses. Malignant cells can disguise themselves as healthy cells, hide where the immune system won’t see them, throw up roadblocks and suppress immune responses.

Sometimes the ongoing battle can leave T cells exhausted and dysfunctional. In addition, many

people with cancer have a weakened immune system due to age, and chemotherapy and radiation can damage immune cells. And some cancers, such as leukemia and lymphoma, affect the immune system itself as abnormal white blood cells grow out of control and crowd out functional ones.

“There’s three ways, in general, that tumors can get around the immune system,” says Jarjour. “One is basically by being invisible. If they don’t have many good targets, the immune system won’t be able to distinguish cancer cells from the normal cells they were derived from. Another is geography. Some tumors are very good at setting up barriers to keep immune cells out. The third is active inhibition of immune cells. There are many ways that tumors do that, and they can leave the immune system pretty bruised and battered.”

The tumor microenvironment presents physical and chemical barriers to T-cell entry and mobility. Tumors may contain a large number of regulatory T cells and tumor-associated macrophages that suppress immune responses. The microenvironment is often hypoxic, or low in oxygen, which impairs T-cell metabolism. Some cancers can hijack immune checkpoints, switches that act as a brake on T-cell activity. The most well known is PD-1, a marker of immune exhaustion on T cells. When PD-1 on T cells binds with the PD-L1 protein on tumors, T-cell activity is turned off; checkpoint inhibitors block this interaction and release the brakes.

The distinction between “hot” and “cold” tumors is a new concept in oncology. Hot, or inflamed, tumors (for example, melanoma and non-small-cell lung cancer) have many mutations and express neoantigens that attract T cells. Cold tumors (for example, ovarian cancer and prostate cancer) are like “immune deserts.”

“A hot tumor is one that is infiltrated by immune cells like T cells, which suggests that the immune system is actively trying to control the cancer. These tumors are more likely to respond to immunotherapy because they just need a nudge in that direction,” explains Maus, whose work involves engineered T cells. “A cold tumor is one that is keeping T cells out and may have cells in it that are especially good at suppressing an immune response.”

Overcoming Immune Evasion

Scientists have come up with numerous approaches to help the immune system recognize and fight cancer. Some stimulate the immune system to work better, while others remove barriers that impede an effective response.

Immunotherapy is not a new idea. Over the centuries, doctors have noticed that tumors may shrink after an infection. In the late 19th century, William Coley—considered the “father of immunotherapy”—observed that some people experienced cancer remission after they developed a severe streptococcal skin infection; he then began administering the bacteria to patients, with mixed results.

Although the intricacies of the immune system were not well understood at the time, from today’s perspective, it appears that the immune response to the bacteria had a collateral effect on cancer.

But inconsistent outcomes, the risks of the procedure and the advent of chemotherapy and radiation therapy put immune-based therapy on the back burner for several decades.

That changed in the 1980s when James Allison, PhD, now at the University of Texas MD Anderson Cancer Center, and others discovered the T-cell antigen receptor and the first immune checkpoint molecule, ultimately leading to the approval of the checkpoint inhibitor Yervoy (ipilimumab) in 2011. Eight checkpoint blockers are now approved for many types of cancer.

While checkpoint inhibitors work well against hot tumors, they aren't very effective against cold tumors that keep immune cells out. So researchers are exploring ways to turn cold tumors hot. "Engineering the T cell itself is a powerful strategy because you can change its genetic code or add in new genes to redirect it or force it to penetrate cold tumors," says Maus.

Approaches to boost T-cell activity include collecting tumor-infiltrating lymphocytes—proven cancer fighters—from a tumor sample, multiplying them in a lab and returning them to the patient. Monoclonal antibodies known as bispecific T-cell engagers attach to a T cell and a tumor protein, bringing the T cell close enough to attack the cancer. CAR-T (chimeric antigen receptor T cell) therapy reprograms a patient's T cells with synthetic receptors that recognize cancer.

Researchers are also developing oncolytic viruses that both kill malignant cells directly and rally a broader immune response as well as vaccines that teach immune cells to recognize cancer neoantigens.

So far, most immunotherapies rely on the adaptive branch of the immune system. But therapies that marshal innate immunity are also in the works, including CAR-NK cells and CAR-macrophages. Because they're not custom-made to target an individual patient's cancer, researchers hope they can be used as off-the-shelf therapies that would be easier and less expensive to produce.

Ultimately, most experts think combination approaches that involve different aspects of the immune response—in effect, releasing the brakes and stepping on the accelerator at the same time—hold the most promise. Old standbys like chemotherapy and radiation can help too, as dying cancer cells release antigens that can spur immune cells into action.

"Looking over the last 20 years, it's remarkable how cancer immunotherapies have broken onto the stage," says Jarjour. "The hope is that we can go from having a subset of patients who are seemingly stably cured of their cancer to expanding that curative treatment to more patients."

Dreamstime

Cells of the Immune System

- Hematopoietic stem cells: progenitor cells that give rise to all types of blood cells
- Neutrophils: abundant short-lived white blood cells that act as first responders, digesting pathogens and releasing cytokines to activate other immune cells
- Eosinophils: innate immune cells mainly responsible for fighting parasites
- Basophils: innate immune cells that release histamine and play a role in allergic reactions and inflammation
- Mast cells: immune cells that play a role in allergic reactions and inflammation
- Monocytes: circulating immune cells that digest pathogens and produce cytokines; when they enter tissues, they evolve into macrophages and sometimes dendritic cells
- Macrophages: immune cells in tissues that engulf pathogens, abnormal cells and cell debris and present antigens to B cells and T cells
- Dendritic cells: immune cells that present antigens to B cells and T cells, serving as a major link between the innate and adaptive immune systems
- Natural killer cells: nonspecific lymphocytes that target virus-infected cells and cancer cells

- B cells: lymphocytes that mature in the bone marrow and evolve into plasma cells, which produce antibodies (humoral immunity)
- T cells: lymphocytes that mature in the thymus gland and are responsible for cellular immunity
- CD4 “helper” T cells: adaptive immune cells that coordinate immune activity, including cytokine production and activation of B cells and CD8 T cells
- CD8 “killer” T cells: adaptive immune cells that destroy virus-infected cells and cancer cells (also known as cytotoxic T lymphocytes)
- Regulatory T cells: cells that dampen immune activity to prevent the immune system from attacking the body (also known as suppressor T cells)
- Red blood cells: cells that carry oxygen-rich blood throughout the body (also known as erythrocytes)
- Platelets: cell fragments responsible for blood clotting (also known as thrombocytes)

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