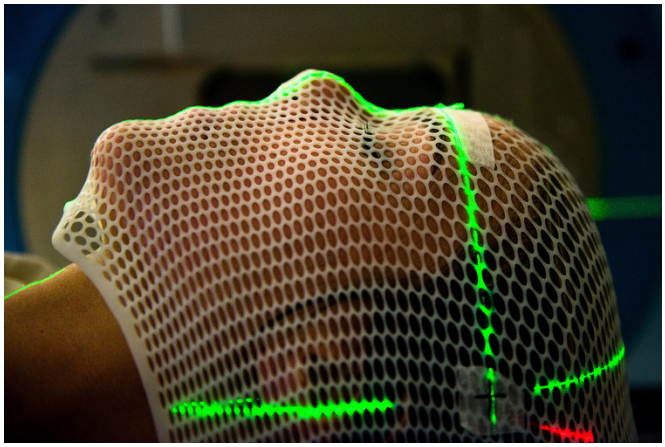
Radiation combined with immune-stimulating drugs could pack a powerful punch against cancer cells

21 March 2016, by Charlie Garnett Benson, Georgia State University



A patient is prepared for radiation treatment at Walter Reed National Military Medical Center. Credit: Airman Magazine/U.S. Air Force photo/Staff Sgt. Russ Scalf/Flickr, CC BY-NC

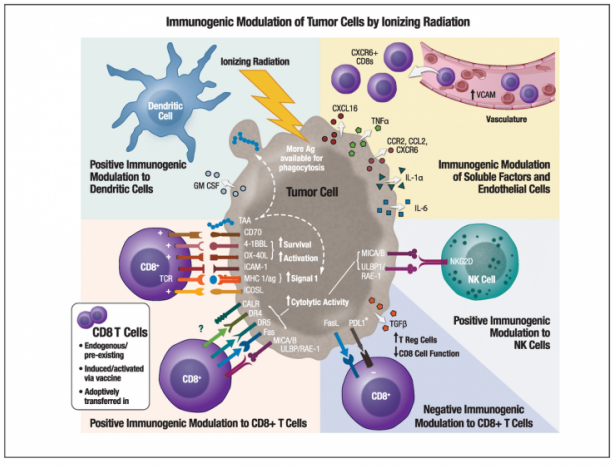
In his final State of the Union address, President Obama tasked Vice President Joe Biden with leading a new National Cancer Moonshot initiative. The hope is that this will put America on course to be "the country that cures cancer once and for all." Listed among the cutting-edge research areas of the initiative is a class of treatments called cancer immunotherapy and combination therapy.

Cancer immunotherapies are treatments that stimulate the immune system to target and attack cancer. Researchers now believe that combining immunotherapy with traditional therapies could open up new possibilities for cancer treatment.

For instance, radiation is one of the oldest and most commonly used forms of cancer treatment out there. But there are limits to how much radiation a person can receive, and it can't kill every cancer cell. However, in combination therapy, radiation could be paired with immunotherapy to pack a one-two punch against cancer cells.

How does radiation kill cancer?

Most cancer patients receive some combination of surgery, chemotherapy and radiation during the course of their care. Radiation is used in about 50 percent of cancer patients. And unlike chemotherapy, which includes hundreds of different drugs that target cancers cells in different ways, ionizing radiation is simply high energy waves. Regardless of how it is delivered, cells generally experience equal doses of radiation in similar ways.



A diagram of Immunogenic Modulation (IM) of Tumor Cells by Ionizing Radiation. Tumors have been reported to be modulated in several ways, which could directly alter the function, activity or recruitment of CD8+ killer T cells, as well as the function of other immune cells. Credit: Charlie Benson, Author provided

Radiation can kill cancer cells directly by damaging their DNA, which then triggers various forms of cell death, including cell suicide (apoptosis). Because the high energy waves can also hit healthy cells around the targeted cancer cells, there's a limit to how high a dose of radiation a person can receive without causing damage to healthy tissue.

Over the years, radiation delivery has improved, allowing more focused delivery to tumors and less damage to surrounding normal cells. Today patients are often treated with smaller doses, separated over time, called fractions. This allows for a higher overall dose to the tumor, but with less of the acute toxic side effects.

But even with these advancements there are still many patients whose cancer isn't cured by radiation alone. Cell suicide, for instance, requires the activity of cellular proteins that trigger the apoptotic process.

Cancer cells can develop mutations in these genes that render them resistant to death from radiation, and these cancer cells escape elimination. Other cancer cells may survive because they receive a sublethal dose due to their location within the tumor.

In some cases, radiation offers no hope of a cure at all. It can still be given, however, to alleviate pain or cause some tumor shrinkage before other treatments are given.

However the cancer cells that survive radiation treatment are not left unaffected. More recently, researchers have realized that zapping cancer cells with radiation can make them better targets for the immune system's own response, and in turn for immunotherapies.

How does immunotherapy fight cancer?

In the early days of immunotherapy, people thought that therapies intended to kill multiplying cells (like radiation and chemotherapy) would never be able to work with an immune-based therapy that is meant to multiply an army of immune cells.

My work and that of others has shown that radiation can make tumor cells express genes that increase the activity of immune cells. This is exciting since many cancer cells evade detection by decreasing the expression of genes that would allow the immune system to recognize and attack the cell. Radiation can reverse this and make cancer cells more noticeable.

For instance, radiation can increase the expression of proteins on the surface of colorectal and prostate tumor cells that increase the survival and killing activity of T cells.

Radiation can also cause cancer cells to release molecules that recruit T cells to the tumor, or stimulate the activity of other cancer-killing cells called natural killer cells.

Many other immune-stimulating genes can be modulated in cancer cells by radiation, called immunogenic modulation, in a variety of cancer cell types. So the old perspective that radiation is wholly immunosuppressive, and can't be used with new immune-based therapies, isn't true after all. So from this immunologist's point of view, I think radiation is still being greatly underutilized.

The addition of radiation to these therapies makes cancer cells better targets for the T cells produced by immunotherapy treatments. And that isn't the only potential benefit of using radiation and immunotherapy together.

Attacking cancer in other parts of the body

Radiation can't target every tumor or every cancer cell in the body. It isn't feasible to deliver radiation to each and every place tumor cells have migrated once the disease metastasizes throughout the body.

That is where a phenomenon called the "abscopal effect" comes in. Abscopal means "away from target," and is a radiation biology term that describes a fascinating phenomenon: sometimes treating a tumor with radiation in one part of the body causes the elimination and cure of a nontreated tumor at a different location.

Many scientists attribute this effect to the activity of

immune cells, triggered by radiation, mounting an effective attack against untreated tumors. This can be shown experimentally in mouse models of cancer. However, it has also been observed in cancer patients in the clinic.

In the past few years, there have been several high-profile reports of abscopal responses in patients with lung, melanoma and other cancers.

This abscopal response occurred even in some melanoma patients receiving radiation just to treat pain. These patients all received some form of cancer immunotherapy in addition to the radiation therapy.

The bad news is that we still aren't sure exactly how to make abscopal responses happen consistently. The challenge is to figure out what exactly is responsible for the abscopal effect so that it can be reproduced reliably in more patients treated with combination therapy.

Questions remain about what the best radiation dose is to cause this effect, the optimal timing to give radiation relative to the cancer immunotherapy, what specific types of cancer are most likely to respond this way and which immunotherapy (from the ever-growing list) is the best for causing this effect in combination strategies.

The overall good news is that radiation has new tricks up its sleeve and can make tumor cells tickle T cells into action. Thus, cancer immunotherapies may help repurpose the use of one of the oldest cancer treatments in new ways.

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