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Sometimes a medical treatment becomes the standard of care before experts are able to explain exactly how or why it works. This is the case with one of the common treatments for aggressive cases of prostate cancer.



Researchers Charles L. Sawyers (left), William Polkinghorn (center) and Simon Powell

For nearly two decades, men with high-risk prostate tumors have been treated with radiation therapy combined with androgen-deprivation therapy (ADT), a class of drugs that blocks the activity of the male sex hormones, which can fuel prostate cancer growth. Now a team from Memorial Sloan Kettering has demonstrated for the first time the mechanism by which these two therapies work together and why the combination helps patients to a much greater degree than either treatment alone.

In addition, their findings might guide further research to develop a test that could be used to determine in advance which patients will benefit from combining ADT with radiation therapy.

“What we determined in this study is at least one mechanism by which androgen deprivation sensitizes prostate cancer cells to the effects of radiation,” says radiation oncologist William R. Polkinghorn, the study’s first author. “For 20 years we have treated high-risk patients with ADT and radiotherapy based upon landmark clinical trials that demonstrated increased survival compared to radiotherapy alone. But now we have, for the first time, a mechanistic explanation for how androgen deprivation sensitizes prostate cancer cells to the effects of radiation.”

Molecular Biology Reveals Function

The investigators, led by senior author Charles Sawyers, Chair of the Human Oncology and Pathogenesis Program, began their study by looking at which genes were activated in tumors that responded to antiandrogen therapy. By studying mouse models of advanced prostate cancer, they determined that many of the androgen-regulated genes encoded for proteins that affect the ability of the cell to repair DNA damage.

Radiation therapy works by damaging the DNA of cancer cells, and cells that are able to evade the effects of radiation may do so because they are able to repair that damage. Drs. Polkinghorn and Sawyers enlisted the help of Sloan Kettering Institute scientists Simon Powell, Jayanta Chaudhuri, and Maria Jasin, world-renowned experts in the study of DNA repair, to explore the mechanisms by which androgen-receptor signaling could affect DNA repair.

Using an experimental model, the team discovered that androgen deprivation primarily affects a DNA repair pathway called non-homologous end-joining.

In the current study, the investigators measured several androgen-receptor-regulated genes and demonstrated that prostate cancers vary dramatically in the activity of those genes. The next question for the team is to determine whether measuring such differences in gene expression levels could make it possible to predict which tumors will respond to combined ADT and radiation therapy.

“The idea is that we could now develop a test to see which patients would benefit from this treatment based on the molecular features outlined in this study,” says Dr. Powell, who is Chair of the Department of Radiation Oncology. “This finding is important for patients, because we don’t want to give them androgen deprivation therapy if it won’t improve outcomes, and instead only give them side effects.”

Side effects of androgen deprivation therapy include loss of libido, weight gain, decreased bone density, diabetes, high blood pressure, and coronary artery disease.

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An Array of Treatment Options

Patients are determined to be high risk, intermediate risk, or low risk based upon certain clinical and pathologic features. High-risk patients are treated more aggressively from the time of diagnosis because their cancers are much more likely to advance and become metastatic.

High-risk patients may choose to undergo surgery instead of radiation and ADT. Previous studies have shown that patients who choose surgery over radiation therapy do not gain from the addition of ADT. This new study explains why the addition of ADT to surgery does not improve outcomes, namely that DNA repair does not affect surgery’s effectiveness.

The current study does not apply to low-risk patients, because they are not given androgen deprivation therapy as part of the standard of care.

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A Paradigm for Hormone Treatment

“Based on the findings in this study, we now think prostate cancer may share more in common with breast cancer than we previously realized,” Dr. Polkinghorn says. “As with breast cancer, there are subsets of patients who will benefit from hormone therapy and others who will not.”

“For many years we have tested breast cancer patients to determine whether their tumors are estrogen receptor positive or negative,” Dr. Powell adds. “We don’t use drugs like tamoxifen or aromatase inhibitors on patients whose tumors are estrogen receptor negative, because we know they won’t benefit.”

“There’s been a lot of focus in the past several years on how to treat advanced, metastatic, castration-resistant prostate cancer, and the recent approval of several drugs for this lethal form of the disease has been paradigm changing,” says Dr. Polkinghorn, who is also an investigator in Dr. Sawyers’s laboratory. Dr. Sawyers has pioneered the development of the next generation of antiandrogen therapies now used to treat castration-resistant prostate cancer.

“But it may be that the best way to treat castration-resistant prostate cancer is to prevent its development in the first place by eradicating all of the disease when the patient is first treated,” Dr. Polkinghorn suggests.

“When this study started in Dr. Sawyers’s lab, there was no expectation that it would go this way,” Dr. Powell concludes. “This is a great example of the kind of research you can do at Memorial Sloan Kettering, where you have people with many different fields of expertise who you can call upon when you need them.”

The study was published in the November issue of the journal *Cancer Discovery*.

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