Tumor-suppressor protein dynamics determine if tissues survive radiation

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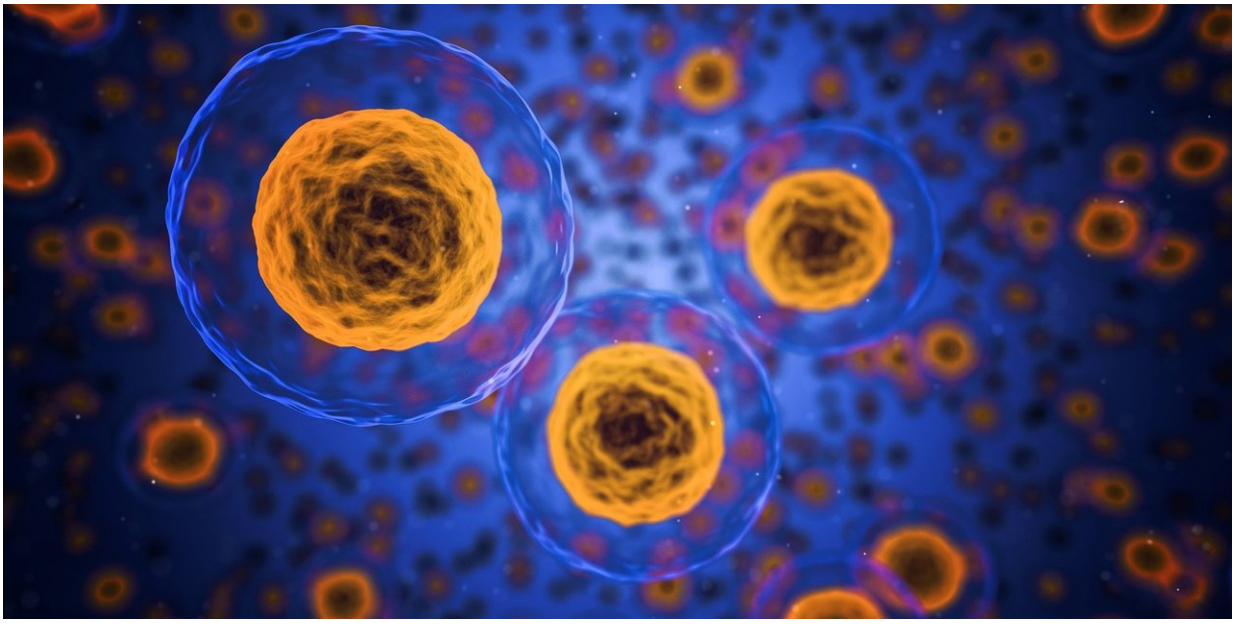

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Exposure to radiation can wreak indiscriminate havoc on cells, tissues, and organs. Curiously, however, some tissues are more vulnerable to radiation damage than others.

Scientists have known these differences involve the protein p53, a well-studied tumor-suppressor protein that initiates a cell's auto-destruct programs. Yet, levels of this sentinel protein are often similar in tissues

with vastly different sensitivities to radiation, posing the question: How is p53 involved?

A new study by researchers in the Blavatnik Institute at Harvard Medical School, Massachusetts General Hospital, and the Novartis Institutes for BioMedical Research now sheds light on this mystery.

Reporting in *Nature Communications* on Feb. 9, they describe how cellular survival after radiation exposure depends on behavior of p53 over time. In vulnerable tissues, p53 levels go up and remain high, leading to cell death. In tissues that tend to survive radiation damage, p53 levels oscillate up and down.

"Dynamics matter. How things change over time matters," said co-corresponding author Galit Lahav, the Novartis Professor of Systems Biology at HMS. "Our ability to understand biology is limited when we only look at snapshots. By seeing how things evolve temporally, we gain much richer information that can be critical for dissecting diseases and creating new therapies."

Notably, the findings suggest new strategies to improve combination therapies for cancer. The team found certain types of tumors in mice were more vulnerable to radiation after being given a drug that blocks p53 levels from declining and oscillating. Tumors treated this way shrunk significantly more than when given either radiation alone or the drug alone.

"We were able to connect differences in temporal p53 expression with radiation response, and these insights allowed us to 'coax' radioresistant tumors into more radiosensitive ones," said co-corresponding author Ralph Weissleder, the Thrall Family Professor of Radiology and HMS professor of systems biology at Mass General. "This is an incredibly exciting study showing that basic science done in rigorous quantitative

fashion can lead to new important clinical discoveries."

When cells are exposed to ionizing radiation, high-energy atomic particles haphazardly assault the delicate molecular machinery inside. If this damage cannot be repaired, particularly to DNA, cells will self-destruct to protect the surrounding tissue and organism as a whole.

This act of cellular seppuku is regulated by p53, which acts as a sentinel for genomic damage. The protein is also a famous tumor suppressor—around half of human cancers have p53 mutations that render it defective or suboptimal. Previously, Lahav and colleagues revealed the dynamic behavior of p53 over time and how it affects cancer drug efficacy, cell fate, and more.

Stronger together

In the current study, Lahav, Weissleder, and their team looked at tissues in mice that have very different sensitivities to ionizing radiation yet are known to express comparable levels of p53—the spleen and thymus, which are highly vulnerable, and the large and small intestines, which are more radioresistant.

Under normal conditions, cells express little to no p53. After radiation exposure, all four tissues expressed elevated p53 along with other markers of DNA and cellular damage as expected. But quantitative imaging analyses revealed that p53 in the intestines peaked and then declined a few hours after irradiation. By contrast, p53 in the spleen and thymus remained high over the same time period.

To probe the effects of p53 behavior, the team used an experimental anti-cancer drug to inhibit MDM2, a protein that degrades p53. They found that by blocking MDM2 activity after radiation exposure, p53 could be forced to remain elevated in cells where it would otherwise decline. In

the intestine, which is normally more resistant to radiation, the addition of the drug reduced cell viability and survival.

Some cancers can become resistant to radiation therapy. So, the team explored whether manipulating p53 dynamics could increase tumor vulnerability, focusing on human colon cancer cell lines with unmutated, functional p53.

In mice with transplanted human colon cancer tumors, the team observed significant tumor shrinkage after a single dose of MDM2 inhibitor given shortly after irradiation. After around 6 weeks, tumors treated with radiation and the drug together were five-times smaller than those treated with the drug alone and half the size of those treated with only with radiation.

"By irradiating first, we force the cancer cells to activate p53, and by adding MDM2 inhibitor on top of that, we can keep p53 active longer," Lahav said. "This combination has a much stronger effect than either alone."

The findings support the importance of understanding the dynamics of p53 and how to manipulate it to treat cancer.

Combination therapies using MDM2 inhibitors are currently being evaluated in clinical trials, the authors note, but these efforts are not designed to examine the underlying mechanisms and timing of the treatments. Further studies are needed to better understand p53 dynamics in cancer, which can inform how to better combine and time therapies to treat patients with cancer.

In addition, although the researchers identified differences in p53 dynamics in different tissues after radiation exposure, the biological pathways that lead to these differences remains a question for future

study.

"For a lab studying p53, cancer is always a major motivation. Our goal is to acquire knowledge to help develop better and more efficient therapies," Lahav said. "Understanding how p53 behaves over time in different conditions is a critical piece of the puzzle."

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Provided by Harvard Medical School

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