Cognitive decline—radiation—brain tumor prevented by temporarily shutting down immune response

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Treating brain tumors comes at a steep cost, especially for children. More than half of patients who endure radiation therapy for these tumors experience irreversible cognitive decline, a side-effect that has particularly damaging consequences for younger patients. Up to now, scientists had been unable to test potential strategies to prevent this problem because there were no laboratory models that faithfully captured the clinical lifecycle of brain tumors.

But in a new study published Nov. 13 in the journal *eLife*, UC San Francisco scientists report the first animal model of glioma—the most aggressive and most common form of brain cancer in the U.S.—that can also be used to study the long-term effects of radiation therapy in tumor-bearing brains. Using this mouse model, the researchers showed that a drug that temporarily suppresses a key component of the brain's immune system can prevent radiation-associated cognitive decline.

The Cost of the Cure

The National Cancer Institute estimates that there will be nearly 24,000 new cases of brain cancer this year. According to Professor of Neurological Surgery Nalin Gupta, MD, Ph.D., radiation therapy is among the most common treatments for these malignancies, but it exacts a tremendous toll.

"Radiation treatment has a significant effect on cognitive function in both children and adults," said Gupta, chief of pediatric neurological surgery at UCSF Benioff Children's Hospital and co-senior author of the new study. "However, age plays a major role and radiation has a much more severe effect on young kids."

Earlier studies have found that young children may experience an eight- to 12-point drop in IQ in the years following radiation treatment. These patients may also exhibit conspicuous changes in behavior.

"If you talk to these kids, they'll speak to you normally," Gupta said. "But they'll have substantial problems with problem solving, retention of long-term memories and executive function. Some show behavioral abnormalities as well—impulsiveness, acting out and bad temper."

To figure out why radiation therapy leads to cognitive impairment, Gupta teamed up with UCSF neuroscientist Susanna Rosi, Ph.D., an expert on the neurological effects of radiation who previously developed mouse models to study how cosmic radiation affects astronauts.

Radiation Turns Immune System from Friend to Foe

Prior work from Rosi's lab found that exposing mice to radiation led to activation of the brain's immune system—in particular, a type of cell known as microglia.

"When the brain's immune system is activated by an insult, like radiation, we generally see that microglia start to affect synapses," said Rosi, professor in the Departments of Physical Therapy and of Neurological Surgery and co-senior author of the new study.

But in mice, the same insult that activates the immune system can also cause it to go haywire.

"Activation of the immune system after an insult like radiation is initially protective," said Rosi. "But with time, instead of resolving, the activation persists and becomes deleterious to the neurons."

In these cases, microglia continue to surveil the brain but no longer limit their search to damaged areas. Instead, they begin to attack healthy brain structures, which results in cognitive impairment. The researchers thought that radiation therapy for brain tumors might be launching the immune system into overdrive in a similar way.

A New Model Emerges

Both the presence of glioma and exposure to radiation are known to activate the brain's immune system, so nobody knew whether immune cells would respond to radiation in the same way in tumor-bearing versus tumor-free brains.

"What we wanted to do in this paper is model what actually happens in patients with brain tumors when you treat those patients with radiation. To do this, we had to develop a mouse model of glioma that recapitulates what occurs in the clinic from the onset of the disease through radiation treatment and beyond," said Gupta, a member of the UCSF Helen Diller Family Comprehensive Cancer Center.

Though mouse models of brain cancer were already available, they harbored an intrinsic flaw: in order to introduce cancer into most mice, researchers have to shut down their immune systems. But given that the immune system plays a major role in both the glioma microenvironment and the brain's response to radiation, models that relied on these so-called immunocompromised mice would not suffice.

Gupta and Rosi devised a way to introduce gliomas into mice without shutting off their immune systems by choosing glioma cells and mouse strains with identical immune profiles, thus allowing the cancer to take hold in immunologically normal mice. Using this model, they were able to study the tumor's biology during and after treatment using a system that more accurately reflects what occurs in the clinic.

Radiation, Not Cancer, Impairs Cognition

Prior to this study, scientists didn't know whether tumors contribute to the cognitive deficits observed in cancer patients, or whether the effects arise solely from irradiation. To probe this question, the researchers performed novel object recognition (NOR) tests—a way to test for cognitive deficits—on two groups of glioma-bearing mice, one that received no radiation treatment, and one that did.

The NOR tests demonstrated that only the irradiated mice had problems forming new memories; the tumor itself seemed to have no effect on cognitive abilities, and Rosi said her previous research suggests an explanation.

"The hippocampus—the brain region in rodents and humans that's involved in forming new memories—is more sensitive to radiation injuries," she explained. "We've used other tests that relate to other cortical structures, and the animals are not impaired. Radiation seems to specifically injure the brain region involved in learning and forming new memories."

A Drug Prevents Cognitive Damage

After establishing that the treatment—not the disease—caused cognitive impairment, the researchers figured out how to prevent the immune system from damaging parts of the brain after radiation therapy.

Rosi's lab had previously shown that a compound called PLX5622, developed by Berkeley, Calif.-based Plexxikon Inc., prevents cognitive damage when administered prior to irradiation. The compound acts by inhibiting a receptor in the brain called CSF-1R, which normally activates the brain's immune system after an injury.

"By using this compound to deplete the immune system at the time of irradiation and allowing it to repopulate on its own afterwards, microglia are no longer primed to alter synapses. If we do this, we can prevent neuronal damage and consequently, prevent the cognitive deficits that develop over time after irradiation," Rosi said.

The researchers administered this compound to tumor-bearing mice prior to radiation treatment and found that they could shrink the tumor without impairing cognition—a result with profound clinical significance if it could be replicated in human patients.

"Ideally, we'd be able to provide this compound to patients prior to their scheduled treatment and prevent cognitive deficits form forming in the first place," Gupta said, adding that he and Rosi hope to move this work into clinical trials.

Another Plexxikon compound that also targets CSF-1R is now being tested in several clinical trials, said Gupta, "and once a drug has completed Phase I trials for another disease, it's relatively easy to get approval to repurpose it for a separate use if you have evidence of its efficacy—which is what we hope our research can provide."

More information: Xi Feng et al. Rescue of cognitive function following fractionated brain irradiation in a novel preclinical glioma model, *eLife* (2018). DOI: 10.7554/eLife.38865

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