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Modified gene targets cancer cells a thousand times more often than healthy cells

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Researchers at the University of Rochester have designed a gene that produces a thousand times more protein in cancer cells than in healthy cells.

The findings may help address the prime challenge in anti-cancer therapy: improving treatments' ability to specifically and effectively target cancer cells. Using this new approach, scientists should be able to insert "self-destruct" codes into the modified gene, forcing cancer cells to kill themselves while healthy cells remain largely unaffected.

Though trials will be necessary to determine if the difference is enough to destroy tumors without harming healthy tissue, the initial findings, published in today's early edition of *Proceedings of the National Academy of Sciences*, are promising, say the authors.

Vera Gorbunova, assistant professor of biology at the University of Rochester, and her team, Andrei Seluanov, assistant professor of biology, and graduate student Christopher Hine, were investigating Rad51, a protein that is expressed at about five times higher level in cancer cells than in healthy cells, when they stumbled on something very unexpected.

"We stripped off some of the Rad51 gene and replaced it with a marker protein DNA to see why Rad51 was five times more abundant in cancer cells," says Gorbunova. "We wanted to see if there was any way we could boost that difference and create a really useful cancer-targeting

tool. We couldn't believe it when we saw the cancer cells expressing the engineered Rad51 around a thousand times more."

When Gorbunova first saw the huge discrepancy, she thought one of her graduate students had fumbled the lab test. Further tests showed that the altered Rad51 was expressed in some cancer cells as much as 12,500 times as often as healthy cells, says Gorbunova. Such a large discrepancy means scientists should be able to use it to create versions of Rad51 that carry a "toxic bomb," which only the cancer cells will trigger.

Rad51 is normally involved in DNA repair, which explains why it's more often expressed in cancer cells. Cancer cells reproduce at accelerated rates, often "not stopping to fix their DNA when they should," says Gorbunova. In these cancer cells, Rad51 is working overtime to repair all the damage, so it's not surprising that it is expressed more often.

Gorbunova believes that when she stripped out part of the Rad51-coding gene, she also stripped out some regulatory elements, which control the production of the protein. Without these elements, healthy cells ignore the gene and do not make the protein. However, these changes have opposite the effect on cancer cells, causing elevated, uncontrolled protein production.

Gobunova and her team have already fused a variant of diphtheria toxin into the Rad51 gene as a "toxic bomb" and tested it on a variety of cancer cell types, including breast cancer, fibrosarcoma, and cervical cancer cells. The results look very promising, she says.

"The early results show the new Rad51 killed all of the cancer cells with minimal if any effect on normal cells," says Gorbunova. "We're very excited. The results are much more striking than anything we would have guessed."

Gorbunova is now working with Stephen Dewhurst, professor of miocrobiology and immunology at the University of Rochester School of Medicine and Dentistry, to design a way to incorporate the new gene with its toxic cargo into a benign virus. If successful, the team will attempt to treat cancer in mice by injecting their tumors with a solution of the virus, and allow the virus to implant the gene into all cells. The key question is whether a dose high enough to kill the cancer cells also will be high enough to kill healthy cells in a living animal, despite the thousand-fold difference in the two cell types' levels of expression.

If the tests are successful, Gorbunova hopes the process might be someday given as a simple shot-in-the-arm, which might travel throughout the bloodstream and stop metastasis in its tracks.

Source: University of Rochester