CRISPR gene editing may halt progression of triple-negative breast cancer

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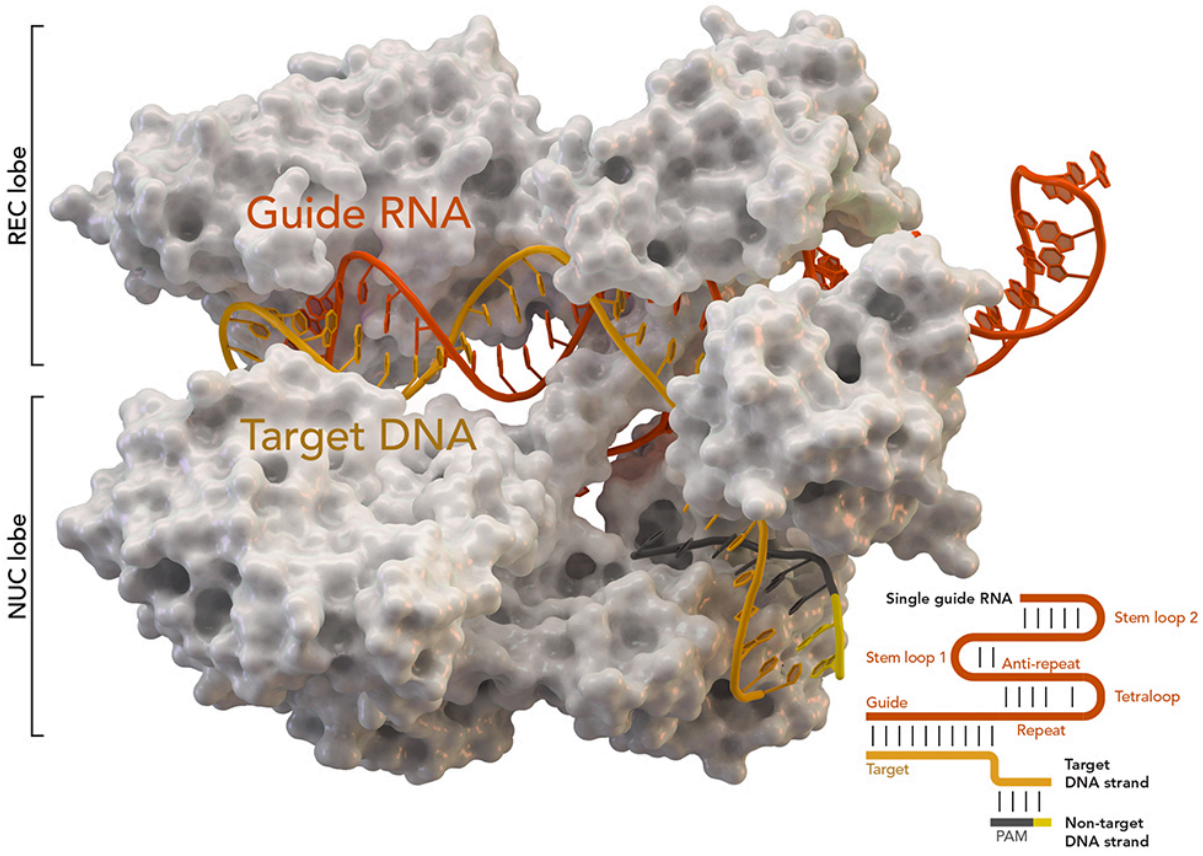

CRISPR-associated protein Cas9 (white) from Staphylococcus aureus based on Protein Database ID 5AXW. Credit: Thomas Splettstoesser (Wikipedia, CC BY-SA 4.0)

A tumor-targeted CRISPR gene editing system, encapsulated in a nanogel and injected into the body, could effectively and safely halt the growth of triple-negative breast cancer, report researchers at Boston Children's Hospital. Their proof-of-principle study, conducted in human tumor cells and in mice, suggests a potential genetic treatment for triple-negative breast cancer, which has the highest mortality rate of all breast cancers.

The new, patent-protected strategy is reported online this week in the journal *PNAS*.

Triple-negative breast cancer (TNBC), lacking estrogen, progesterone and HER2 receptors, accounts for 12 percent of all breast cancers. It occurs more frequently in women under age 50, in African American women, and in women carrying a BRCA1 gene mutation. Surgery, chemotherapy, and radiotherapy are the few treatment options for this highly aggressive, frequently metastatic cancer, which is in urgent need of more effective targeted therapeutics.

The new study, led by Peng Guo, Ph.D., and Marsha Moses, Ph.D., in the Vascular Biology Program at Boston Children's, represents the first successful use of targeted CRISPR gene editing to halt growth of a TNBC tumor in vivo (via injection into live, tumor-bearing mice). The new system is non-toxic and utilizes antibodies to selectively recognize cancer cells while sparing normal tissues.

Experiments showed that the CRISPR system was able to home in on breast tumors and knock out a well-known breast-cancer promoting gene, Lipocalin 2, with an editing efficiency of 81 percent in tumor tissue. The approach attenuated tumor growth by 77 percent in the mouse model and showed no toxicity in normal tissues.

Precision delivery of CRISPR

To date, translating CRISRP gene editing technology into disease therapies has been limited by the lack of effective CRISPR delivery systems. One method uses a virus to deliver the CRISPR system, but the virus cannot carry large payloads and potentially can cause side effects if it "infects" cells other than those targeted. Another method encapsulates the CRISPR system inside a cationic polymer or lipid nanoparticles, but these elements can be toxic to cells, and the CRISPR system is often trapped or broken down by the body before it reaches its destination.

The new approach encapsulates the CRISPR editing system inside a soft "nanolipogel" made up of nontoxic fatty molecules and hydrogels. Antibodies attached to the gel's surface then guide the CRISPR nanoparticles to the tumor site. The antibodies are designed to recognize and target ICAM-1, a molecule the Moses Lab identified in 2014 as being a novel drug target for triple-negative breast cancer.

Because the particles are soft and flexible, they can more efficiently enter cells than their stiffer counterparts. While stiffer nanoparticles can get trapped by the cell's ingestion machinery, the soft particles were able to fuse with the tumor cell membrane and deliver CRISPR payloads directly inside the cell.

"Using a soft particle allows us to penetrate the tumor better, without side effects, and with bigger cargo," says Guo, the study's first author. "Our system can substantially increase tumor delivery of CRISPR."

Once inside the cell, the CRISPR system knocked out Lipocalin 2, an oncogene that promotes breast tumor progression and metastasis. Experiments showed that loss of the oncogene inhibited the cancer's aggressiveness and tendency to migrate or metastasize. The treated mice showed no evidence of toxicity.

Although the study focused on triple-negative breast cancer, Moses

believes the team's CRISPR platform could be adapted to treat pediatric cancers as well, and could also deliver conventional drugs. These studies are ongoing. The team is in discussions with a number of companies interested in the technology.

"Our system can deliver significantly more drug to the tumor, in a precise and safe way," Moses says.

More information: Peng Guo el al., "Therapeutic genome editing of triple-negative breast tumors using a noncationic and deformable nanolipogel," *PNAS* (2019). www.pnas.org/cgi/doi/10.1073/pnas.1904697116

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