New cancer immunotherapy approach turns human cells into tiny anti-tumor drug factories

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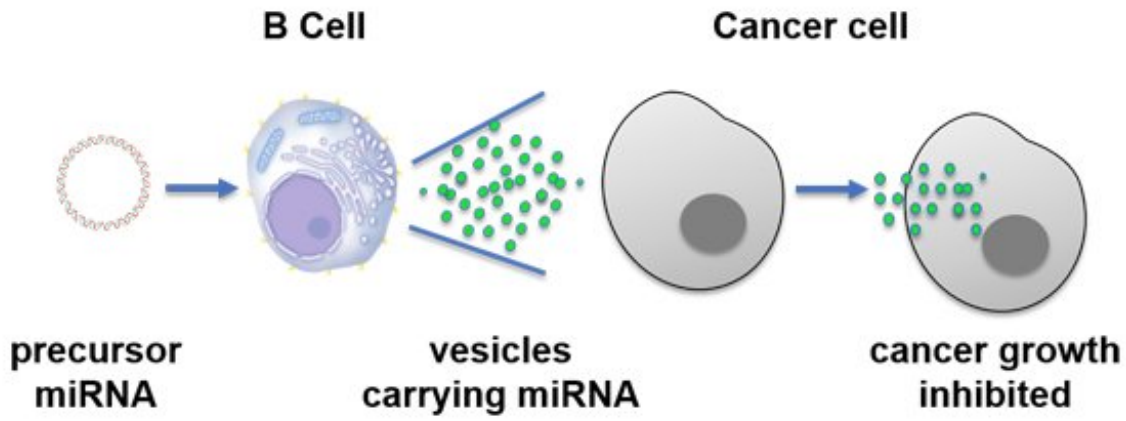

UC San Diego School of Medicine researchers developed a method to use B cells to manufacture and secrete microRNA-containing vesicles and showed they can inhibit tumor growth in mice. Credit: UC San Diego Health

Cancer immunotherapy—efforts to better arm a patient's own immune system to attack tumors—has shown great potential for treating some cancers. Yet immunotherapy doesn't work for everyone, and some types of treatment can cause serious side effects.

In a new approach, researchers at University of California San Diego School of Medicine are turning B cells, best known for producing

antibodies, into factories that assemble and secrete vesicles or sacs containing microRNAs. Once internalized by cancer cells, these small pieces of genetic material dampen a gene that spurs tumor growth. In mice, breast tumors treated with this approach were fewer and significantly smaller than in untreated tumors.

The study is published in the December 4 issue of *Scientific Reports*.

"Once further developed, we envision this method could be used in situations where other forms of immunotherapy don't work," said senior author Maurizio Zanetti, MD, professor of medicine at UC San Diego School of Medicine and head of the Laboratory of Immunology at UC San Diego Moores Cancer Center. "The advantages are that this type of treatment is localized, meaning potentially fewer side effects. It's long-lasting, so a patient might not need frequent injections or infusions. And it would likely work against a number of different tumor types, including breast cancer, ovarian cancer, gastric cancer, pancreatic cancer and hepatocellular carcinoma."

MicroRNAs don't encode proteins. Instead, microRNAs bind messenger RNAs that do encode proteins, inhibiting their translation or hastening their degradation. Normal cells use microRNAs to help fine-tune which genes are dialed up or down at different times. MicroRNAs tend to be less active in cancer cells, which can allow growth-related proteins to run wild.

In this study, Zanetti and team used miR-335, a microRNA that specifically dampens SOX4, a transcription factor that promotes tumor growth. They added a miR-335 precursor to B cells in the lab. Once inside, through a naturally occurring process, the cells convert the precursor into mature, active miR-335 and package it into vesicles, small, membrane-coated sacs that bud off from the cell. Each B cell can produce 100,000 miR-335-containing vesicles per day—enough to treat

10 cancer cells.

To test this new system, the researchers treated human breast cancer cells with miR-335-containing vesicles or sham vesicles in the lab. Then they transplanted the cancer cells to mice. After 60 days, 100 percent (5/5) of the mice with mock-treated cancer cells had large tumors. In contrast, 44 percent (4/9) of the mice with miR-335 vesicle-treated cancer cells had tumors. On average, the tumors in the treated mice were more than 260 times smaller than those in the mock-treated mice (7.2 vs. 1,896 mm3).

And the treatment was long-lasting—miR-335 levels were still elevated in the treated mice 60 days after the vesicles and cancer cells were transplanted.

"We were surprised to find that even small changes in cancer cell gene expression after miR-335 treatment were associated with specific down-regulation of molecules key to tumor growth," said study co-author Hannah Carter, Ph.D., assistant professor of medicine at UC San Diego School of Medicine.

Other research groups and pharmaceutical companies are using tumor suppressor microRNAs therapeutically. What's new here, said researchers, is the method for producing and delivering them.

According to Zanetti, this therapy could be developed in two ways. First, by first harvesting vesicles from B cells in a lab, then administering only the vesicles, as they did here, or second, by administering the B cells themselves. He says the challenge now will be to develop ways to ensure the B cells or vesicles get as close to a tumor as possible. This would be easier in some types of cancer, where the tumor is readily accessible by injection. But many cancers are difficult to access. Zanetti and colleagues are currently working to improve the delivery system,

maximize efficiency and diminish side effects.

"Ideally, in the future we could test patients to see if they carry a deficiency in miR-335 and have an overabundance of SOX4," Zanetti said. "Then we'd treat only those patients, cases where we know the treatment would most likely work. That's what we call personalized, or precision, medicine. We could also apply this technique to other microRNAs with other targets in cancer cells and in other cell types that surround and enable tumors."

More information: Gonzalo Almanza et al. Extracellular vesicles produced in B cells deliver tumor suppressor miR-335 to breast cancer cells disrupting oncogenic programming in vitro and in vivo, *Scientific Reports* (2018). DOI: 10.1038/s41598-018-35968-2

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