Gobbling up poison: A method for killing colon cancer

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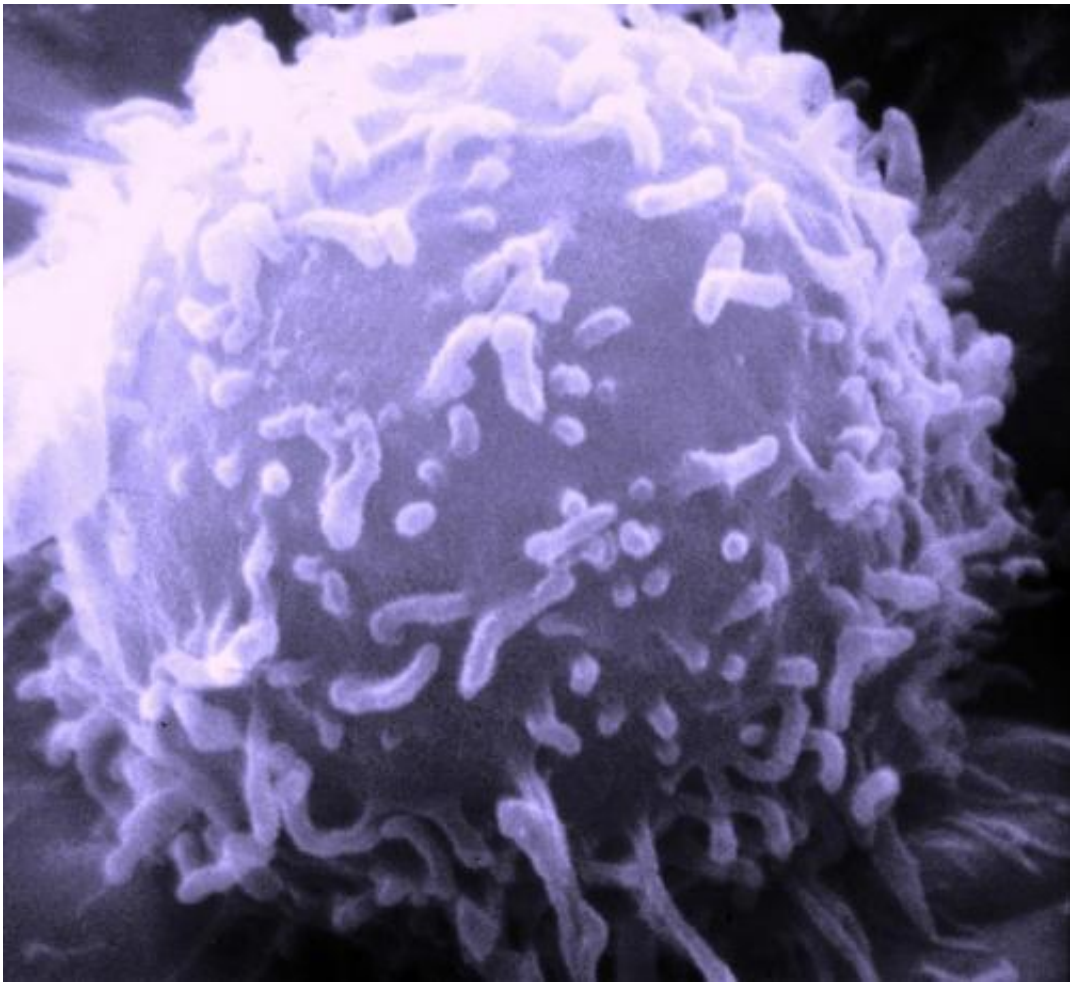

Electron microscopic image of a single human lymphocyte. Credit: Dr. Triche National Cancer Institute

These days, cancer researchers aim to design targeted and specific therapy – those that kill cancer but spare the surrounding tissue. Immunotoxins, which use cancer-targeted antibodies linked to deadly toxins such as ricin, are one such therapy. However, few have succeeded to date in part because cancer cells share many molecules with normal cells, and because it can be challenging to unlock the deadly chemical only after the antibody has homed to the diseased tissue.

Now researchers at Thomas Jefferson University have discovered the unique biological properties inherent to colon cancer that make it a perfect candidate for immunotoxins – an antibody that won't attach to normal cells and a toxin-delivery system that takes advantage of a fluke of biology: Colon cancer cells will gobble up poison if it's attached to a key receptor on the cell's surface. Indeed, the researchers demonstrated that the novel immunotoxin they created could reduce the lung metastasis in mice, which had grown out from colon cancers, by more than 80 percent with only 6 doses, in research published September 8th, 2014 in the journal *Oncotarget*.

"These studies pave the way for effective antibody-directed therapy for metastatic disease in colorectal cancer, which currently carries a greater than 90 percent chance of mortality" says Scott Waldman, M.D., Ph.D., Chair of the Department of Pharmacology & Experimental Therapeutics and the Samuel MV Hamilton Professor at Thomas Jefferson University.

Dr. Waldman's laboratory first discovered that the colon cancer receptor GUCY2C (pronounced by the researchers as "goosy toosy") would act as a homing signal in 1993. Although GUCY2Y also is expressed by normal cells, not just colon cancers, the normally expressed receptors are "hidden" from the immune system in the so-called immunoprivileged sites of the brain and the surface of the digestive tract that faces the food and water.

Researchers assumed that the GUCY2C receptor was over-produced and exhibited on the surface of cancer cells. Instead, this work shows the GUCY2Y receptors are quickly gobbled back up into the cancer cells in membrane-bound sacs called endosomes that fuse with vesicles carrying digestive or acidic fluid called lysosomes.

Once a toxin-bound antibody attaches to GUCY2C on either primary colon cancers or metastases throughout the body, the cancer cells will internalize the receptor – antibody, ricin and all. Once the endosomes fuse with the acid-containing lysosomes that digest the linker molecule, the free toxin destroys the cancer cell from the inside with little collateral damage.

This finding is key, says Dr. Waldman, because it provides design parameters for creating immunotoxins with various agents. The immunotoxin Dr. Waldman used was an antibody against GUCY2C bound to the active portion of the ricin molecule with a chemical linker that degrades in acidic environments. However, other deadly toxins that could be kept inactive by the linker molecule could be coupled to the antibody, traveling throughout the body without causing damage until they are taken up by colon cancer metastases.

And the therapy wouldn't be limited to colon cancer. Gastric, esophageal and pancreatic cancers also express GUCY2C molecules, suggesting that the immunotoxin approach could be effective against the difficult-to-treat metastases in those diseases as well.

In fact, the concept is currently being tested in a phase II clinical trial for gastric, esophageal and prostate cancers by Millennium Pharmaceuticals, a Takeda Oncology Company.

More information: G.P. Marszalowicz "GUCY2C lysosomotropic endocytosis delivers immunotoxin therapy to metastatic colorectal

cancer," *Oncotarget*, 2014.