Study identifies new targeted treatment strategy for some aggressive cancers

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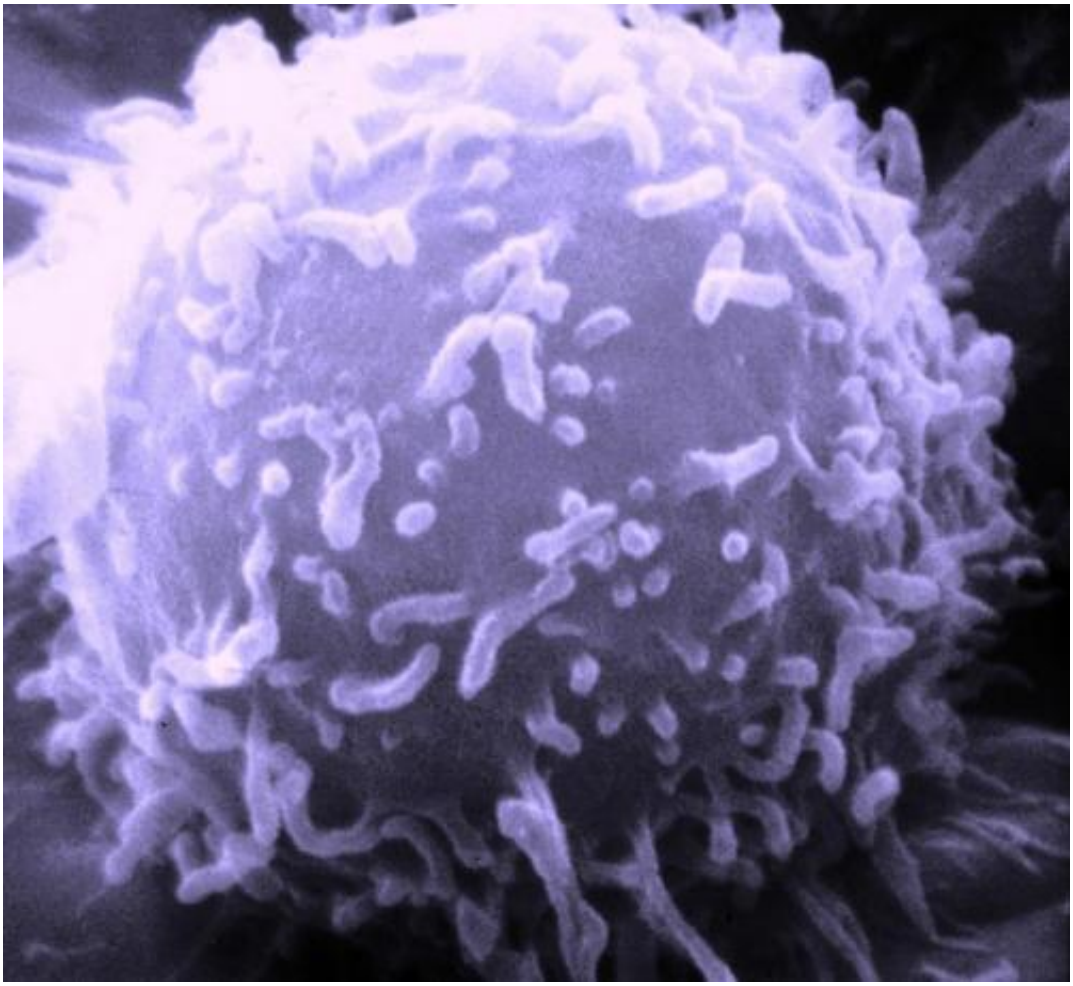

Electron microscopic image of a single human lymphocyte. Credit: Dr. Triche National Cancer Institute

Researchers from the Massachusetts General Hospital (MGH) Cancer Center and Boston University School of Medicine (BUSM) have identified the first potential treatment targeting a pathway by which several aggressive tumors maintain their ability to proliferate. Treatment with a small molecule that blocks a key step in that pathway - the alternative lengthening of telomeres (ALT) pathway - was able to inhibit the growth and survival of ALT-positive tumor cells.

"Identification of genetic markers that predict cancer cell vulnerabilities and new drugs to exploit such vulnerabilities is a focal point of cancer research today," says Lee Zou, PhD, associate scientific director of the MGH Cancer Center, senior and co-corresponding author of the report in the Jan. 16 issue of *Science*. "Cancer cells must rely on either the telomerase enzyme or the ALT pathway to bypass the normal processes of cell aging and death. Our findings may provide a new direction for the treatment of ALT-positive cancers - which include osteosarcoma, glioblastoma and certain pancreatic tumors."

Telomeres are repetitive DNA sequences that sit at the ends of chromosomes and serve a protective function to make sure cells do not lose valuable genetic information each time they divide. When telomeres have been eroded to a critically short length, they send out a signal to the cell telling it to stop dividing, ensuring that the genetic information remains intact but limiting the cell's lifespan. Cancer cells have evolved to overcome this constant attrition by continuously extending those eroded telomeres, promoting cellular immortality.

There are two major pathways for telomere elongation in cancer cells. The more common pathway relies on the enzyme telomerase to extend telomeres. The less understood ALT pathway lengthens telomeres through recombination with DNA sequences from other chromosomes.

In their investigations, the researchers studied how the action and

expression of several key proteins is altered in cancer cells that use the ALT pathway. Focusing on a protein called ATR, a master regulator of DNA repair and recombination, the investigators verified that the protein also plays a crucial role in regulating the ALT pathway. They found that the ATR inhibitors VE-821 and AZ20 selectively eliminated ALT-positive osteosarcoma and glioblastoma cells from panels of cancer cell lines, suppressing their ability to extend their telomeres though recombination and leading to the cells' death.

Co-corresponding and lead author Rachel Flynn, PhD, assistant professor of Pharmacology & Experimental Therapeutics and Medicine at BUSM, explains, "This study suggests that inhibiting ATR may be a novel and important strategy in treating cancers that rely on the ALT pathway, including up to 60 percent of osteosarcomas and 40 to 60 percent of glioblastomas. Such targeted treatments would only affect cancer cells and have little effect on the surrounding healthy tissue, potentially minimizing the harsh and debilitating side effects experienced with traditional cancer therapies." Flynn began the project as a postdoctoral fellow in Zou's MGH Cancer Center lab and completed the investigation after joining the faculty at BUSM.

While clinical trials of telomerase inhibitors for the treatment of cancer are currently underway, the up to 10 percent of tumors that do not use the telomerase pathway would not respond to such drugs. "Testing tumors for their use of telomerase or the ALT pathway is not yet routine," Flynn says. "If VE-821 or other ATR inhibitors are clinically successful, it would support such testing and may lead to more personalized and targeted therapeutic regimens for several cancers refractory to traditional chemotherapeutics."

More information: "Alternative lengthening of telomeres renders cancer cells hypersensitive to ATR inhibitors," by R.L. Flynn www.sciencemag.org/lookup/doi/ … 1126/science.1257216

Provided by Massachusetts General Hospital