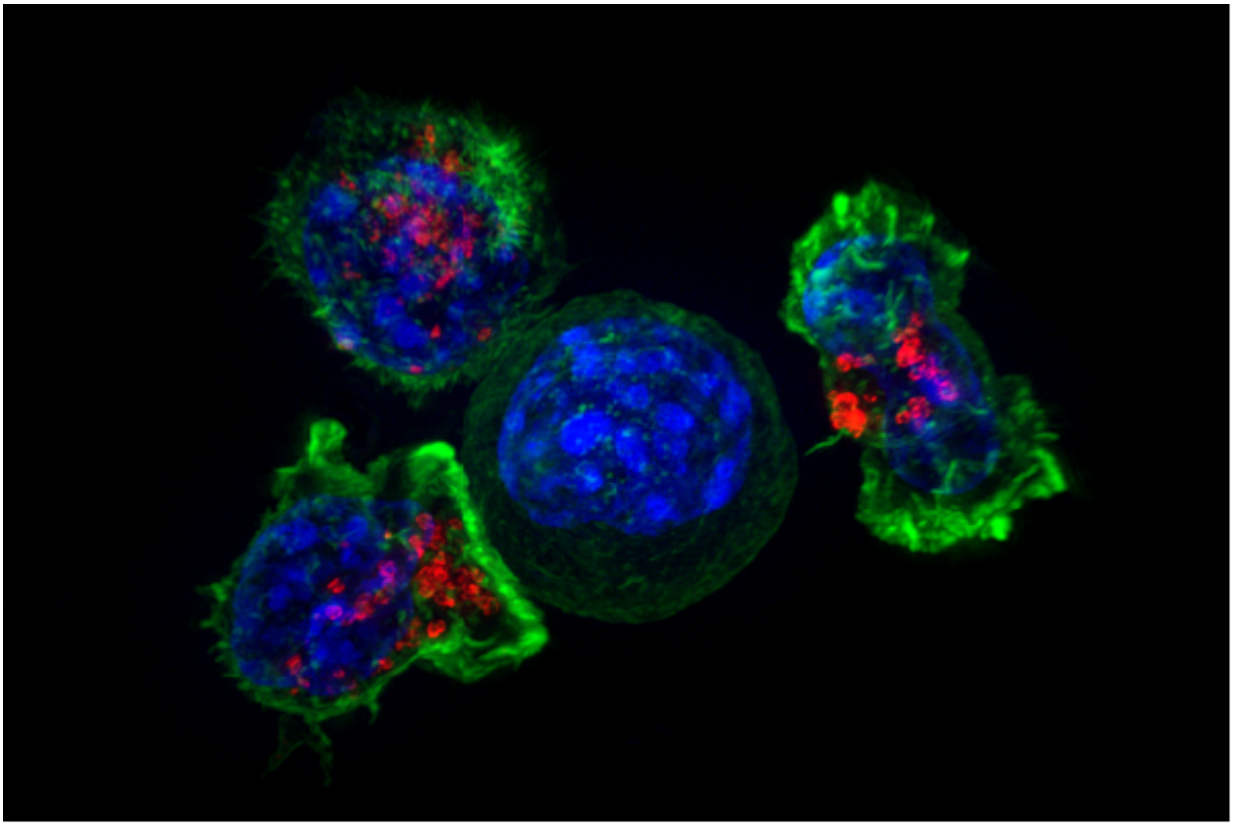
MedicalXpress

Proposed cancer treatment may boost lung cancer stem cells, study warns

November 20 2018



Killer T cells surround a cancer cell. Credit: NIH

Epigenetic therapies—targeting enzymes that alter what genes are turned on or off in a cell—are of growing interest in the cancer field as a way of making a cancer less aggressive or less malignant. Researchers at Boston

Children's Hospital now report that at least one epigenetic therapy that initially looked promising for lung cancer actually has the opposite effect, boosting cancer stem cells that are believed to drive tumors. They also identify a strategy that reduces these cells, curbing lung cancer in mice.

Findings were published online today in *Nature Communications*.

Cancer stem cells have been identified in blood cancers and a variety of solid tumors. They make up a tiny fraction of tumor cells, but can regenerate a cancer on their own. Carla Kim, Ph.D., and colleagues in Boston Children's Hospital's Stem Cell Research program have shown that cancer stem cells play a role in adenocarcinoma, the most common type of lung cancer. When they transplanted cancer stem cells from a diseased mouse, previously healthy mice developed lung cancer.

The new study, led by lab member Samuel Rowbotham, Ph.D., looked at an epigenetic therapy that inhibits the enzyme G9a, a type of histone methyltransferase. G9a had been thought to be cancer-promoting, and some studies have suggested that inhibiting G9a is an effective strategy in certain cancers, including adenocarcinoma. Rowbotham and Kim now call this into question.

"People had looked at cell lines from lung tumors and found that they are sensitive to drugs inhibiting G9a," says Rowbotham, first author on the paper. "In general tumor cell populations, these drugs would slow down growth or even kill the cells. But we found that these drugs were also making the surviving tumor cells more stem-like. We predicted that this would advance disease progression, and this is what we saw."

The team first looked at adenocarcinoma cell lines and found that when the cells were treated with G9a, they became more like stem cells. They then transplanted cancer stem cells into live mice and tracked the

development of adenocarcinoma. When they knocked down the G9a gene in lung tumors, the tumors grew bigger and spread farther.

Kim believes this down side to G9a hadn't been noticed because prior studies only looked at cell lines, and because cancer stem cells are hard to detect.

"Earlier studies couldn't see that cancer stem cells were still around, and there's more of them when you treat with these drugs," she says. "Because they're such a small fraction of the tumor, anything that affects them can easily be missed."

A new epigenetic target?

But Rowbotham, Kim and colleagues also found potentially better enzymes to target: Histone demethylases. Their action is chemically opposite to that of G9a, stripping off a methyl group from histone where G9a adds one. When Rowbotham knocked down the gene for demethylase enzymes, and added drug that prevents them from working, he was able to make the cells look less like cancer stem cells in a dish and behave less like cancer stem cells in live mice. When he gave demethylase inhibitors to mice with established lung tumors, cancer progression was slowed and the animals survived longer than untreated mice.

Although a cancer stem cell hasn't been found in human adenocarcinoma, Kim believes the findings are worth pursuing further. She notes a related line of evidence—a 2017 study that found that demethylase inhibitors were effective in killing chemotherapy-resistant cells from patient tumors.

"Even if we can't pinpoint cancer stem cells in human patients, Sam's work shows you can start by studying a cancer stem cell in a mouse

model and identify targets that could be clinically important," she says. "It shows the importance of finding the right molecule the cancer is sensitive to. In adenocarcinoma, a demethylase inhibitor is likelier to be more useful than methyltransferase inhibitor."

They and others envision a two-phase strategy for adenocarcinoma that would first target the general population of cancer cells to "debulk" the tumor, then add a second treatment specifically directed at cancer stem cells.

The team is now doing further studies to explore demethylase inhibitors as potential therapeutic drugs, alone or in combination with other treatments. Because demethylase inhibitors have very broad effects, they will also look for genes the inhibitors affect downstream, which could provide more specific drug targets.

Provided by Children's Hospital Boston