Path to a Targeted Treatment for Small-Cell Lung Cancer?

A common mutation makes mouse tumors more vulnerable to certain cancer drugs.

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Small-cell lung cancer is aggressive and deadly, and progress is long overdue: Patients with SCLC have been treated with the same chemo regimen for 30 years. Could a precision medicine approach deliver patients a much-needed new option? In a new study, scientists at Fred Hutchinson Cancer Research Center reveal how losing a specific gene — which happens in about 15 percent of SCLC patients — accelerates tumor formation in mice. And, most exciting to the researchers, these tumors seem to be uniquely sensitive to a specific drug, which dramatically shrunk some tumors in mice with the mutation.

The drug, known as an HDAC inhibitor, is currently in clinical trials to treat patients with other cancers. The findings "suggest that HDAC inhibitors could have a role in treating small-cell lung cancer if directed to the right subsets of small-cell patients," said David MacPherson, PhD, a lung cancer researcher and senior author on the study, published today in Cancer Discovery.

Verifying a new tumor suppressor in small-cell lung cancer

Each year in the U.S., small-cell lung cancer makes up about 10 to 15 percent of lung cancer diagnoses, or about 35,000 patients. Lung tumors are generally divided into non-small cell lung cancer and small-cell lung cancer. Compared to NSCLC, the most common type of lung cancer, SCLC is more likely to spread, or metastasize, from the lungs to other areas of the body. About 30 percent of patients diagnosed with early-stage SCLC will survive five years. But most are diagnosed with metastatic disease; for these patients, the five-year survival rate is just 2 percent.

MacPherson wants to change this. He believes that more tailored treatment options are most likely to give SCLC patients the treatment advances they need.

"The goal of my lab is to understand the biology of different subsets of small-cell lung cancer, and to identify unique vulnerabilities that might be applicable to each genetic subset of small-cell," he said.

In the current study, MacPherson and his team, together with collaborators in Kwon-Sik Park, PhD's lab at the University of Virginia, focused on a gene called CREBBP, which encodes a protein that

helps keep other genes turned on. The gene for CREBBP is mutated in about 15 percent of SCLC tumors, making it one of the most commonly altered genes in this disease. But SCLC tumors carry many mutations. Does CREBBP play any role in blocking tumor formation, or are the mutations a red herring?

To learn more, he and his team turned to a strain of mice that are prone to small cell lung cancer. In some of these mice, the researchers inactivated CREBBP; in others, they left CREBBP alone. Then, they compared the growth of the cancer in both groups of mice. Without CREBBP, SCLC tumors came on faster and were more deadly. In these mice, it took 384 days for half the mice to develop tumors, compared to 444 days in mice with normal CREBBP.

Inactivating CREBBP also accelerated tumors seeded from human SCLC patients.

“We clearly showed that when we inactivate CREBBP in multiple model systems, we accelerate small-cell lung cancer. It’s definitively a functional tumor suppressor in small-cell lung cancer,” MacPherson noted.

The researchers saw similar effects when they disabled CREBBP in mouse models of other neuroendocrine tumors, of which SCLC is just one type. This suggested that it may play a similar role across this broad category of tumors, which can arise in a number of organs, including the lung, pancreas and colon.

CREBBP regulates cell adhesion genes

How does CREBBP help cells resist tumor formation? To answer this question, MacPherson and his team took advantage of CREBBP’s similar role among several types of neuroendocrine tumors. Their studies focused on CREBBP’s role in keeping genes turned on. When CREBBP is no longer active, its target genes will get turned off or will be turned on at lower levels.

The group discovered a core group of genes that were turned down when CREBBP was removed. These included many that maintain tight contacts between cells, including one known as E-cadherin. This protein helps cells in solid tissues stick together — a hurdle that cells must overcome to leave the original tumor and metastasize.

CREBBP influences DNA packaging. Each of our cells contains nearly six feet of DNA that must be carefully packaged to keep it neat and untangled. To assist this tidiness, proteins called histones act as spools around which our DNA winds like thread. Tighter DNA packaging helps turn genes off, while looser DNA bundling helps turn them on. CREBBP loosens bundled DNA — and helps keep genes on — by adding molecules known as acetyl groups to the histones.

When MacPherson and his team looked more closely at the cell-adhesion genes they had pinpointed, they saw that in cells lacking CREBBP, these genes’ histones had many fewer acetyl groups.

This is the first time that CREBBP has been shown to regulate cellular adhesion, MacPherson

noted. This is likely because his team examined its role in a solid tumor, in which connections between cells help prevent them from spreading through the body. Although others have studied CREBBP's role as a tumor suppressor, it has been in the context of blood cancers, in which solitary cancer cells spread through the body and the lack of cellular connections does not play a role in tumor progression.

Potential targeted treatment

Discovering how CREBBP works was only the first step. Next, MacPherson hoped that this knowledge would point him in the direction of a potential treatment for patients with this type of tumor. Because CREBBP is missing in these cells, his team cannot directly target it. But knowing CREBBP's general role — keeping DNA open and accessible — suggested to him that they could try a drug that produced a similar effect.

He turned to a drug called a histone deacetylase (HDAC) inhibitor, which, like CREBBP, works to keep DNA loosely packed. It ensures that the acetyl groups that make DNA bundling nice and spacious stay on histones. The result is that genes stay turned on, too.

MacPherson and his team tested Pracinostat, an HDAC inhibitor that is in clinical trials for treating patients with other types of cancer. They saw that, indeed, Pracinostat treatment increased acetylation of histones in SCLC cells lacking CREBBP. This correlated with increased expression of CREBBP targets like E-cadherin.

The researchers also looked at whether Pracinostat could halt or reverse SCLC tumors in their mice, comparing tumors with and without functional CREBBP. Pracinostat made tumors with normal CREBBP stop growing in six of eight animals, decreased tumor size in one animal, and had no effect in the last animal.

In contrast, Pracinostat treatment produced dramatic responses in several of the animals with CREBBP-inactivated tumors. In four of the 12 mice, tumors shrunk dramatically or even disappeared. In five other animals, tumor growth stalled. In the other three, the drug had no apparent effect.

Next steps

The results do suggest that precision medicine may hold hope for therapeutic advances against SCLC, though much work remains to be done. MacPherson noted that even among mice with CREBBP-mutated tumors, responses to Pracinostat varied, and he aims to learn more about what distinguishes tumors that responded exceptionally well and those that did not. These lessons will be important for further tailoring HDAC treatment if it proves promising for SCLC treatment.

Genes that encode proteins that act similarly to CREBBP are also commonly mutated in SCLC. MacPherson, who is also studying their role in SCLC, suspects that tumors with these alterations may also be particularly vulnerable to HDAC inhibitors.

Finally, MacPherson and his team are hunting for other weaknesses in tumors with inactivated CREBBP. By working as broadly as possible, he hopes to identify completely new avenues for this subset of SCLC, and to help usher in much needed targeted treatments for this disease.

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