Researchers find experimental therapy turns on tumor suppressor gene in cancer cells

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Researchers at Mayo Clinic have found that the experimental drug they are testing to treat a deadly form of thyroid cancer turns on a powerful tumor suppressor capable of halting cell growth. Few other cancer drugs have this property, they say.

In the Feb. 15 issue of *Cancer Research* (available online Jan. 20), they report that RS5444, being tested in a Phase 1/2 clinical trial to treat anaplastic thyroid cancer, might be useful for treating other cancers. The agent is also known as CS-7017.

From previous research, the investigators knew that RS5444 binds to a protein known as PPAR-gamma, a transcriptional factor that increases the expression of many genes. They had found that human anaplastic thyroid tumor cells treated with RS5444 expressed a protein known as p21, which inhibited cell replication and tumor growth. But they did not understand how. They have now discovered that the agent actually forces PPAR-gamma to turn on the RhoB tumor suppressor gene, which in turn induces p21 expression.

"This is very unusual," says the study's lead investigator, John Copland, Ph.D., a cancer biologist at the Mayo Clinic campus at Jacksonville. "Drugs typically target genes and proteins that are over-expressed and turn them off. We found that RS5444 turns on a valuable tumor suppressor gene. We rarely find a drug that can take a suppressed gene and cause it to be re-expressed."

This finding suggests that other cancers in which RhoB is deactivated might respond to RS5444 or to similar drugs, says co-author Robert Smallridge, M.D., who treats thyroid cancer patients at Mayo Clinic in Jacksonville.

"This study provides a hint that this class of drugs could have a significant effect on cancer biology because of its action on this tumor suppressor gene," says Dr. Smallridge.

According to Dr. Copland, "RS5444 and other so-called PPAR-gamma drugs, which were originally created to treat diabetes because they help regulate glucose metabolism, are in development or being tested as cancer therapies. Taken orally, RS5444 requires 1,000-fold less dosage than current Food and Drug Administration-approved drugs in this class of compounds to inhibit tumor growth."

The researchers have been seeking to identify and characterize the molecular mechanisms underlying the cause and progression of human anaplastic thyroid carcinoma. Their goal is to develop effective molecular targeted therapies.

This cancer is extremely rare — fewer than 600 cases are diagnosed in the U.S. annually — but may be better known of late because it may have been the type of thyroid cancer that led to the death of William Rehnquist, chief justice of the United States. "It is also one of the most aggressive and deadliest known cancers, since it doesn't respond to any known treatment," says Dr. Smallridge. "The rate of survival hasn't changed in 25 years. Eighty-five percent of patients die within a year of diagnosis."

In previous work, the investigators identified a combination of drugs that reduced tumor size in animal models, strongly implicating that this regimen might benefit patients with the cancer. RS5444, developed by

Daiichi Sankyo, Co., Ltd., in Japan, was one agent tested in combination with chemotherapy. Sankyo researchers discovered RS5444 in a screen for antitumor activity and then sought help from Mayo Clinic Cancer Center to further study its properties.

Their encouraging findings in preclinical studies led to the launch of a multicenter Phase 1/2 clinical trial, testing use of RS5444 and paclitaxel chemotherapy in patients with the cancer. The study, led by Dr. Smallridge, is being conducted at Mayo Clinic campuses in Jacksonville and Rochester, Minn. and at eight other sites nationally.

clinicaltrials.gov/ct2/show/NCT00603941?intr=
%22CS7017%22&rank=1

This study was designed to look at the specific signaling pathways within anaplastic thyroid cancer cells that are disrupted by RS5444. Researchers had thought that because PPAR-gamma was mutated in a subset of thyroid cancers, PPAR-gamma might be acting as a tumor suppressor gene, and that turning it back on restored that function. This hypothesis made sense, because PPAR-gamma is a powerful nuclear receptor that activates genes involved in such cellular processes as differentiation, apoptosis, cell-cycle control, carcinogenesis, and inflammation.

But they found that PPAR-gamma regulates transcription of the RhoB gene. "Within several hours of administering the drug, we can see that it binds to the PPAR-gamma protein in cancer cells and activates RhoB transcription, causing expression of RhoB messenger RNA that is translated into protein. By a yet-to-be-identified mechanism, RhoB then induces the transcription of p21, thereby shutting down the cell cycle and blocking tumor growth," Dr. Copland says.

"That shows us that turning RhoB back on may be a key mechanism for

regulating growth of this cancer," he says.

For proof, the researchers then turned off expression of RhoB in cells that were treated with the drug, and demonstrated that p21 could not be activated. "That shows RhoB is required for p21 transcription," Dr. Copland says.

"RhoB acts as a tumor suppressor, and it is turned off in anaplastic thyroid cancers. Turning this gene back on may lead to an effective molecular targeted chemotherapy regimen to fight this cancer," he says.

Dr. Smallridge adds, "Hitting this pathway inhibits tumor growth up to fourfold in laboratory cells and in animal experiments, and we are optimistic that it could be one cancer pathway capable of manipulation in patients. We hope there are other cancers in which RhoB is silenced, such as head and neck, brain, and lung cancers, that could benefit as well where RhoB has been shown to be down-regulated in patient tumor tissues."

Source: Mayo Clinic