U-M researchers discover gene switched off in cancer can be turned on

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A gene implicated in the development of cancer cells can be switched on using drugs, report researchers from the University of Michigan Comprehensive Cancer Center. The finding could lead to a new class of targeted cancer therapies with potential to benefit many different cancer types.

Popular new drugs such as Herceptin and Gleevec more effectively treat cancer by targeting genetic mutations that express themselves in large amounts, causing cancer to develop. But cancers also arise because genes that control growth are turned off. While researchers can use these turned-off genes to identify or monitor cancer, currently no treatments actually target these genes.

U-M researchers found that a gene called Brahma, or BRM, is silent – but not missing – in some cancer cells. By exposing the BRM protein to an inhibitor drug, the researchers were able to turn the gene back on, allowing BRM to be expressed. The researchers found this gene is turned off in about 15 percent of tumors studied, including cells from lung, esophageal, ovarian, bladder, colon and breast cancers.

The researchers were able to use existing drugs, which showed some usefulness in turning on the BRM gene. But new drugs would need to be developed to be more effective in reactivating this gene in cancer cells. Still, researchers are excited about the potential this finding could have in leading to new targets for cancer treatment.

“This is a targetable target. We can detect it, but we need to find a better way to turn it back on. No drugs are designed to deal with a gene that’s turned off. But it’s a straightforward extension of current therapies that target genes that are turned on,” says lead study author David Reisman, M.D., Ph.D., assistant professor of internal medicine at the U-M Medical School.

Results of the study appear in the advanced online publication of the journal Oncogene.

The researchers sought to understand why BRM is not expressed in certain cancer cell lines. They found no mutations to the gene but rather that it was just silent – essentially like a switch that had been turned off. Knowing that a class of drugs called histone deacetylase inhibitors, or HDAC inhibitors, can affect gene expression, the researchers applied these drugs to the cells and found the BRM expression could be restored – like flipping the switch back on.

While the existing HDAC inhibitors did return BRM expression, the effect was short-lived. Once the drugs were taken away, BRM expression decreased.

“The HDAC inhibitors are not the perfect answer, but in principle this tells us we can turn our gene back on. If we can turn the gene back on, it may not be a cure for cancer, but it could slow it down or make it responsive to existing drugs,” Reisman says.

The researchers targeted lung cancer cell lines in particular, although they found similar results in a variety of other cancer cell lines tested. A potential target to treat lung cancer is particularly crucial as the death rate from lung cancer has not changed in 30 years. Newer treatments are much less toxic and extend lives by months, but the same people who died from lung cancer 30 years ago, would still succumb to this disease

today.

Targeted therapies have dramatically improved cancer care in recent years, because they thwart the specific genes which drive the development and progress of cancers. They typically have few toxic side effects, unlike traditional chemotherapy, making them more tolerable as a long-term treatment or in combination with other drugs.

“Tumors are not the same from one person to the next, and even the cells within a single tumor are not the same. Giving a single drug or drug combination to 500 people is setting ourselves up for failure, much like a one-size-fits-all clothing store would never succeed,” Reisman says.

“Targeted therapies are now opening the door, because they are essentially given only to those patients who have a high likelihood of response. Their low toxicity means the patient can be treated for long periods of time, which is unlike older and more traditional chemotherapy agents. Even if these new targeted therapies don’t cure the cancer, we can at least have long-term survival,” he adds.

Source: University of Michigan Health System