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Study suggests new approach to fight lung cancer

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Recent research has shown that cancer cells have a much different – and more complex – metabolism than normal cells. Now, scientists at The University of Texas at Dallas have found that exploiting these differences might provide a new strategy to combat lung cancer.

In an article published online May 21 in the journal *PLOS ONE*, UT Dallas researchers compared the metabolic characteristics of non-small-cell lung cancer cells with normal lung cells taken from the same patient.

They found that the cancer cells consumed substantially more oxygen than normal cells, about two and a half times as much. The lung cancer cells also outpaced their normal counterparts in synthesizing a critical chemical called heme.

Heme is an iron-containing molecule that is a component of a variety of hemoproteins, which transport, store and use oxygen throughout the body, among other functions. These proteins directly regulate many processes involved in oxygen metabolism, converting oxygen to the energy that cells need to thrive. For example, heme binds to and transports oxygen to cells via the familiar hemoglobin protein.

"We reasoned that the enhanced oxygen consumption we found in lung cancer cells might be attributable to increased levels of heme and hemoproteins," said Dr. Li Zhang, professor of molecular and cell biology at UT Dallas and senior author of the paper.

To test this possibility, Zhang and biology graduate student Jagmohan Hooda measured and compared the levels of heme that lung cancer cells synthesize and the amount that normal lung cells make.

"All cells need a certain level of heme, but our findings indicate that normal cells need much less heme compared to cancer cells," Zhang said. "We think a high level of heme in cancer cells results in a lot more hemoproteins, which metabolize oxygen and produce more cellular energy. That then drives the cancer cells to proliferate, to migrate and to form colonies.

"Cancer cells not only make significantly more heme, we also found they uptake more heme from the blood," said Zhang, who holds the Cecil H. and Ida Green Distinguished Chair in Systems Biology Science.

Zhang and Hooda then treated the matched set of lung cancer and normal lung cells with a heme inhibitor called succinyl acetone. The chemical blocks cells from synthesizing heme.

Other researchers have previously studied the ability of succinyl acetone to inhibit growth of various types of cancer cells, but until the UT Dallas study, Zhang said it was not known whether those effects were unique to cancer in general or how the compound might affect normal cells.

"Before our study, scientists didn't know whether there was any difference in effect between cancer cells and normal cells," Zhang said. "Now we know that this compound doesn't have much effect on normal cells, but it does have an effect on lung cancer cells."

Inhibiting the cancer cells' ability to produce heme affected those cells dramatically, said Hooda, who was the lead author of the study.

"Suppressing heme availability reduced the lung cancer cells' ability to

use oxygen, and hence the cells' ability to proliferate and migrate," he said. "The cultured cancer cells we studied stopped proliferating and eventually died."

Zhang said a key finding was that normal cells don't need that much heme to function properly.

"When you inhibit heme synthesis or deplete heme, it doesn't affect normal cells too much," she said. "It selectively affects cancer cells. That's the beauty of our work.

"Because inhibiting heme effectively arrested the progression of lung cancer cells, our findings could positively impact research on lung cancer biology and therapeutics."

The National Cancer Institute estimates that 228,000 new cases of lung cancer will be diagnosed and more than 159,000 deaths from the disease will occur in the U.S. in 2013.

Although more research is needed before new therapies might be developed from the findings, Hooda said the heme-inhibiting technique would likely not be toxic to humans, noting that succinyl acetone would not need to eliminate all heme synthesis in the body.

"Even after lowering heme levels to the point that cancer cells are affected, it's likely that normal cells would live on with a small amount of heme," Hooda said.

Provided by University of Texas at Dallas