

Lung cancer cells' survival gene seen as drug target

One of the deadliest forms of cancer appears to carry a specific weakness. When a key gene called 14-3-3zeta is silenced, lung cancer cells can't survive on their own, researchers have found.

The gene is a potential target for selective anti-cancer drugs, says Haiyan Fu, PhD, professor of pharmacology, hematology & oncology at Emory University School of Medicine and Emory Winship Cancer Institute.

The research results will be published the week of Dec. 24 in the *Proceedings of the National Academy of Sciences*. The paper's first author is Zenggang Li, PhD, a postdoctoral fellow in Dr. Fu's laboratory.

Lung cancer kills more Americans annually than any other type of malignancy, according to the National Cancer Institute. Yet treatment options are very limited, Dr. Fu says.

"The recent trend towards targeted therapies requires us to understand the altered signaling pathways in the cell that allow cancer to develop," he says. "If you think about genes that are dysregulated in cancer as drivers or passengers, we want to find the drivers and then, aim for these drivers during drug discovery."

Dr. Fu and his collaborator, Fadlo Khuri, MD, deputy director of clinical and translational research at Emory Winship Cancer Institute, chose to focus on the gene 14-3-3zeta because it is activated in many lung tumors. In addition, recent research elsewhere shows that survival of lung cancer patients is worse if the gene is on overdrive in their tumors, Dr. Fu says.

14-3-3 genes are found in mammals, plants and fungi. In the human body, they come in seven flavors, each given a Greek letter. Scientists describe the proteins they encode as adaptors that clamp onto other proteins. The clamping function depends on whether the target protein is phosphorylated, a chemical switch that regulates processes such as cell division, growth, or death.

"We knew that 14-3-3 is important in controlling EGFR (epidermal growth factor receptor) signaling, which is a main pathway driving lung cancer," Dr. Fu says. A couple of recently introduced drugs that were shown to be effective against lung cancer target EGFR, he adds.

In the PNAS study, the authors used a technique called RNA interference to selectively silence the 14-3-3zeta gene. They found that when 14-3-3zeta is turned off, lung cancer cells become less able to form new tumor colonies in a laboratory test.

One of the most important properties of cancer cells is their ability to grow and survive without touching other cells or the polymers that connect them. While the authors found that the cells with 14-3-3zeta turned off do not grow more slowly, the cells are vulnerable to anoikis (Greek for homelessness), a form of cell death that happens when non-cancerous cells that are accustomed to growing in layers find themselves alone.

Further experiments showed that 14-3-3zeta regulates a set of proteins called the Bcl2 family that control programmed cell death, and its absence upsets the balance within the family.

"You can see how control of anoikis means 14-3-3zeta could play a critical role in cancer invasion and metastasis," Dr. Fu says. "The mechanistic question we still haven't answered is: what makes zeta unique so that it can't be replaced by the others."

The finding has implications beyond lung cancer, in that 14-3-3zeta is also activated in other forms of cancer such as breast and oral, he notes.

"Dr. Fu and his team's findings unmask the role of 14-3-3 zeta in the survival advantage of lung cancer cells and their dependence on it," Dr. Khuri says. "Targeting this critical molecule could lead to meaningful therapeutic progress."

Since 14-3-3zeta was identified as a promising target for drugs, Dr. Fu and his co-workers are making use of a robot-driven screening program at the Emory Chemical Biology Discovery Center to sort through thousands of chemicals that may disrupt its interactions specifically.

They hope to identify these compounds rapidly and move them from bench into clinic testing to benefit patients.

Source: Emory University

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