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Gene fusion shifts cell activity into high gear, causing some cancer

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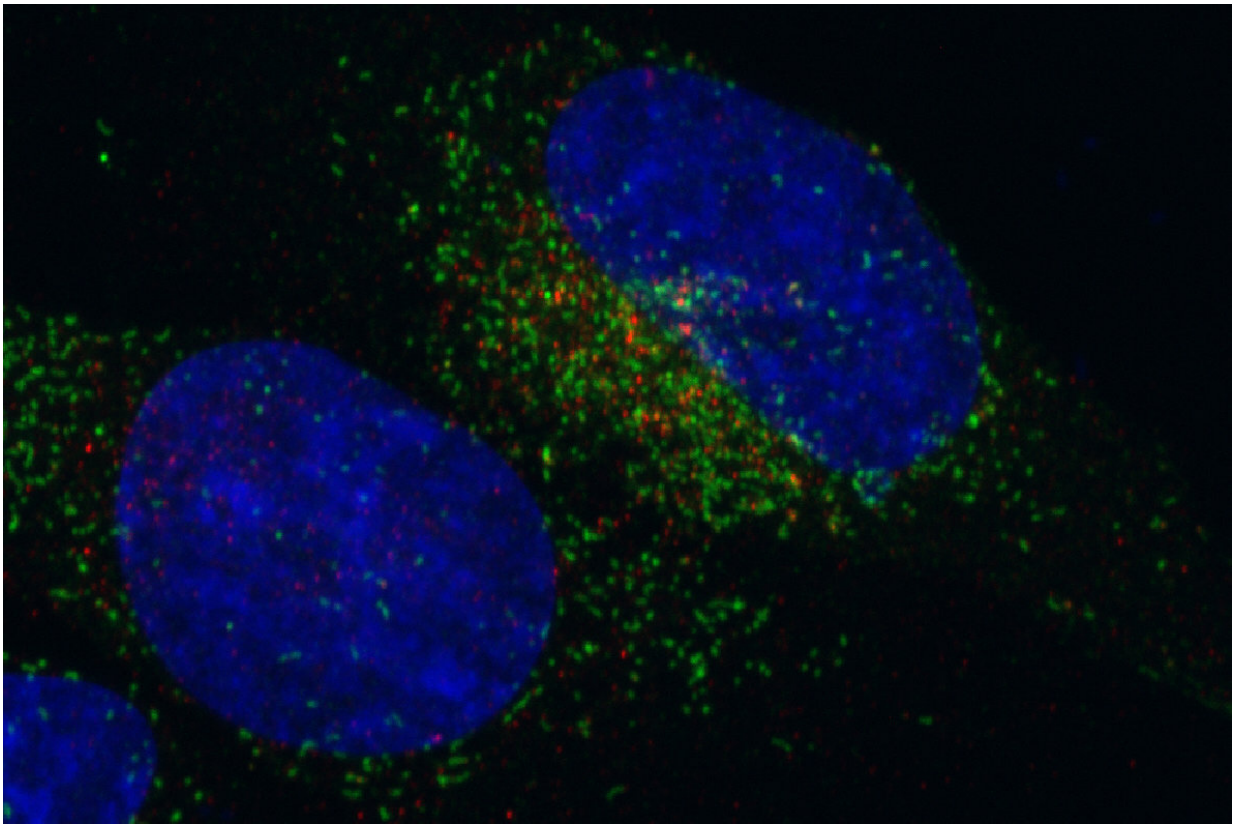

Central nervous system cells expressing the FGFR3-TACC3 fusion protein. Credit: Iavarone Lab, Columbia University Medical Center

The fusion of two adjacent genes can cause cancer by kicking mitochondria into overdrive and increasing the amount of fuel available

for rampant cell growth, researchers at Columbia University Medical Center (CUMC) have discovered. They also found that drugs that target this newly identified cancer pathway can prevent tumor growth, both in human cancer cells and mice with a form of brain cancer.

The study was published online today in the journal *Nature*.

In a 2012 study published in Science, the CUMC team found that some cases of glioblastoma, the most common and aggressive form of primary brain cancer, are caused by the fusion of two genes, FGFR3 and TACC3. At the time, it was thought that this gene fusion was limited to a fraction of brain tumors, affecting about 300 patients in the U.S. per year.

Since then, however, other researchers have observed the same gene fusion in a percentage of lung, esophageal, breast, head and neck, cervical, and bladder cancers, affecting tens of thousands of cancer patients overall. "It's probably the single most common gene fusion in human cancer," said study co-leader Antonio Iavarone, MD, professor of neurology and of pathology and cell biology (in the Institute for Cancer Genetics) at CUMC. "We wanted to determine how FGFR3-TACC3 fusion induces and maintains cancer so that we could identify novel targets for drug therapy."

Changes in mitochondria—the 'powerhouse' of the cell—have been observed in cancer for a long time, but researchers have found only recently that mitochondrial activity and cellular metabolism are linked to certain cancers. However, the mechanism by which genetic mutations alter mitochondrial activity and promote tumor growth was unknown.

In the current study, the CUMC researchers compared the activity of thousands of genes in cancer cells with and without FGFR3-TACC3. They discovered that the fusion greatly increases the number and

accelerates the activity of mitochondria. Cancer cells, which require huge amounts of energy to rapidly divide and grow, can thrive when mitochondrial activity has been amped up.

Using a variety of experimental techniques, the researchers determined that the gene fusion initiates a cascade of events that increases mitochondrial activity. First, FGFR3-TACC3 activates a protein called PIN4. Once activated, PIN4 travels to peroxisomes, cellular structures that break down fats into substances that fuel mitochondrial activity. Activated PIN4 triggers a four-to-five-fold increase in the production of peroxisomes, which release a flood of oxidants. Finally, these oxidants induce PGC1alpha, a key regulator of mitochondrial metabolism, to increase mitochondrial activity and energy production.

"Our study offers the first clues as to how cancer genes activate mitochondrial metabolism, a crucial and longstanding question in cancer research, and provides the first direct evidence that peroxisomes are involved in cancer," said study co-leader Anna Lasorella, MD, professor of cell biology (in the Institute for Cancer Genetics) and of pediatrics at CUMC. "This gives us new insights into how we may be able to disrupt cancer's fuel supply."

In another experiment, treating human brain cancer cells containing FGFR3-TACC3 with mitochondrial inhibitors interrupted the production of energy inside cancer cells and significantly slowed tumor growth. The same effect was seen in a mouse model of human brain cancer containing this gene fusion.

Dr. Iavarone suspects that a dual-treatment approach may be needed for patients with FGFR3-TACC3 tumors. In their previous study, the researchers found that drugs that inhibit FGFR3 kinase, an enzyme that helps the protein produced by this fusion gene do its work, increased survival when tested in mice with glioblastoma.

These drugs are now being tested in patients with recurrent glioblastoma that contains the gene fusion by one of the paper's co-authors, Marc Sanson, MD, of Pitié Salpêtrière Hospital in Paris. "Drugs that inhibit active kinases have been tried with encouraging results in some cancers," said Dr. Iavarone. "But invariably, they become resistant to the drugs, and the tumors come back. However, it may be possible to prevent resistance and tumor recurrence by targeting both mitochondrial metabolism and FGFR3-TACC3 directly."

Based on the findings in this study, the team is now considering the possibility of adding mitochondrial inhibitors into the therapeutic mix for patients in this trial.

The CUMC team is currently testing this dual approach in human cancer cells and animals models.

More information: A metabolic function of FGFR3-TACC3 gene fusions in cancer, *Nature* (2018). nature.com/articles/doi:10.1038/nature25171

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