

# Scientists discover 2 genes that drive aggressive brain cancers

December 23 2009

---

A team of Columbia scientists have discovered two genes that, when simultaneously activated, are responsible for the most aggressive forms of human brain cancer.

This finding was made possible by the assembly of the first comprehensive network of molecular interactions that determine the behavior of these [cancer](#) cells, a map so complex and elusive that, until now, it could not be constructed. The discovery may lead to completely novel strategies to diagnose and treat these incurable tumors.

The findings will be published in an advanced online edition of Nature on Dec. 23, 2009, by a team of Columbia scientists led by Antonio Iavarone, M.D., associate professor of neurology in the Herbert Irving Comprehensive Cancer Center, and Andrea Califano, Ph.D., director of the Columbia Initiative in Systems Biology.

The researchers studied a type of human malignancy, called glioblastoma multiforme, which is among the most lethal because it rapidly invades the normal brain producing inoperable [brain tumors](#). Recently, glioblastoma claimed the life of Senator Edward Kennedy only sixteen months after diagnosis.

Before this study, cancer researchers had little idea why glioblastoma is so aggressive. "We now know that two genes - C/EPB and Stat3 - are the disease's master 'control knobs'," said Dr. Iavarone. "When simultaneously activated, they work together to turn on hundreds of

other genes that transform [brain cells](#) into highly aggressive, migratory cells."

The two genes are active in about 60 percent of all glioblastoma patients and help identify poor-prognosis patients. All patients in the study whose tumors showed activation of both factors died within 140 weeks after diagnosis, while one half of the patients without these factors were still alive.

"The finding means that suppressing both genes simultaneously, using a combination of drugs, may be a powerful therapeutic approach for these patients, for whom no satisfactory treatment exists," said Dr. Califano.

This approach, called combination therapy, is supported by this study since silencing both genes in human glioblastoma cells completely blocked their ability to form tumors when injected in a mouse. Based on these results, the Columbia scientists received a grant from the American Recovery and Reinvestment Act to develop drugs specifically aimed at these genes.

## **Two Genes Uncovered with a Systems Biology Approach**

Biomedical researchers today are like city engineers trying to reduce traffic jams without a street map. Armed only with a list of congested roads, engineers would not be able to locate the traffic jams or find the best way to unclog them. But with a city map in hand, clusters of congestion would immediately become apparent along with possible solutions.

"We are fighting very much the same problem in the post-genomic era," said Dr. Califano. "The human genome project has given biologists a

wonderfully comprehensive list of street names - the genes inside every human cell. Unfortunately, it provided virtually no understanding of how all those genes may work together, within highly complex control networks, to operate the cell. In short, biologists need a map of the cell."

Thirty years of laboratory experimentation have revealed glimpses of the complete network. Yet, with trillions of potential interactions among our genes and different network structures in different cells, experimentation alone is unlikely to succeed. Best estimates indicate that only 10 percent of all the molecular interactions in a cell are understood and only a very small fraction of them in any specific cell type.

The Columbia team, which includes physicists and biologists, has for the first time assembled and experimentally validated such a cellular network for a glioblastoma cell, a hugely complex challenge that required several novel approaches drawn from the fields of information theory and computational biology.

"Armed with such a blueprint of the cell machinery, we can now ask pointed questions, such as which genes are responsible for the most deadly features of these tumors," said Dr. Iavarone.

From this blueprint, produced in Dr. Califano's lab, the scientists pinpointed the tumor's two master regulator genes. Experiments conducted by Dr. Iavarone in brain [cancer cells](#) and mice then confirmed the accuracy of the network and the importance of the two genes.

## **Discovery Accelerates Search for Better Treatments, Changes How Scientists Investigate Disease**

"The identification of C/EPB and Stat3 came as a complete surprise to us, since these genes had never been implicated before in brain cancer,"

said Dr. Iavarone. Based on traditional approaches, their critical role may have eluded researchers for a long time.

"From a therapeutic perspective, it means we are no longer wasting time developing drugs against minor actors in [brain cancer](#)," added Dr. Iavarone. "We can now attack the major players."

Given its generality, the new approach has the potential to change the way researchers think not just about cancer but also about many other diseases.

In the last decade, reams of data have been generated by the human genome project and new high-throughput technologies that measure the activity of each gene inside a cell. Yet, the way cancer biologists evaluate this data seemed very biased to the Columbia scientists. Typically, researchers compare data from cancer cells and normal cells and focus on the genes with the greatest change in activity.

It's like investigating a plane crash and blaming the wing because it has the most damage. The actual alterations that caused the crash - like the causes of cancer - may be far more subtle, like a tiny defective control circuit that shows almost no damage.

Instead of focusing on the "damaged wings" of cancer, the new network approach allows biologists to pinpoint causal genes by tracing their downstream effects back to the source.

Indeed, in the case of glioblastoma, the activity of the two master [genes](#) was virtually identical in cancer cells compared to normal cells. Yet, like a tiny control switch causing a plane crash, their combined effect turned out to be massive.

Provided by Columbia University Medical Center

Citation: Scientists discover 2 genes that drive aggressive brain cancers (2009, December 23)  
retrieved 10 April 2024 from

<https://medicalxpress.com/news/2009-12-scientists-genes-aggressive-brain-cancers.html>

<p>This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.</p>
--