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Data-handling technique finds genes to be team players in curbing brain cancer cell growth

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The search for cancer genes is increasingly a matter of molecular "To Tell the Truth," as scientists seek to distinguish genes actually involved in the disease from those that are imposters. Powerful gene-scanning technology often reveals hundreds or thousands of genetic irregularities in tumor tissue, making it critical for investigators to winnow out the true culprits.

In a new study in the April 8 issue of the journal *Cancer Cell*, researchers at Dana-Farber Cancer Institute and Memorial Sloan-Kettering Cancer Center describe a new algorithm for ranking abnormal genes according to their likelihood of contributing to a cancer. And they show that a gene identified by the algorithm as a likely restrainer of tumor growth does indeed play that role in a common type of brain cancer, and is not a mere "bystander" to another restrainer gene.

"As the Human Cancer Genome Project begins to map the genetic alterations in different kinds of cancer, we need to be able to discriminate between alterations that truly are relevant to the disease and those that are not," says the paper's senior author, Lynda Chin, MD, of Dana-Farber. "Using a new algorithm developed in collaboration with Cameron Brennan, MD, of Memorial Sloan-Kettering, we were able to identify genes with too many or too few copies in cancer cells."

The algorithm can be used to analyze similar genomic data generated by

The Cancer Genome Atlas pilot project, a federally-led effort to explore genomic changes involved in human cancer. It is also being submitted to BioConductor, a collection of open-source computational tools for free download by researchers.

The Cancer Cell paper describes how the algorithm was applied to a study of glioblastoma, the most common form of brain cancer in adults and one of the most difficult malignancies to treat successfully. Chin and her colleagues performed high-resolution genomic scans of glioblastoma tumor samples and cell lines, and the results showed dozens of gene copy alterations, some of which had already been linked to the disease and some of which had not. To determine which of these “suspect” alterations were most likely to contribute to cancer, the researchers ran the results through their new algorithm.

One of the highest-scoring abnormalities -- meaning it had a high potential to cause rampant cell growth -- involved a gene known as p18INK4C. Researchers knew that one of p18INK4C’s cousins, a tumor-restraining or – suppressing – gene called p16INK4A, is missing in a majority of glioblastoma cases. p18INK4C itself, however, wasn’t previously known to be missing in the disease. Although the two genes are thought to have similar functions, investigators suspected the co-disappearance was more than a coincidence, and that the loss of p18INK4C plays a role in glioblastoma.

Based on the algorithmic analysis, lead author Ruprecht Wiedemeyer, PhD, a postdoctoral fellow in Chin’s lab, went in search of a connection between p16INK4A and p18INK4C that can explain their joint disappearance. It turns out that the loss of p16INK4A triggers a shutdown of a “pathway” (a series of interconnected genes) called RB. That, in turn, causes cell proliferation and a giant step toward cancer. At that point, p18INK4C steps in as a backup system, pulling the reins on the hectic cell growth permitted by the loss of p16INK4A. If p18INK4C

is lost, it's as though the emergency brake on growth is gone.

"We found that p16 and p18 are part of a 'feedback' loop that keeps the growth of normal glial cells in check," Chin states. "When p16 goes out of commission, p18 is signaled to pick up the slack. We demonstrated that the deletion of both genes is required for glioblastoma to develop."

The feedback loop is the latest evidence that cancer gene pathways are not as straightforward as scientists once thought them to be. "Just a few years ago, the view was that pathways were largely linear," Chin comments. "We're increasingly coming to appreciate, however, that they operate in concert – that each one has multiple tentacles reaching out to other pathways and they function collectively as a network. When one pathway goes out of commission, another may switch on to compensate." Such knowledge means that effective treatment of cancers cannot rely on inhibiting single pathways, but must anticipate how the network would react.

The algorithm was designed as a reliable way of determining which gene alterations are most likely linked to cancer. It filters data from gene-array studies through a "three-dimensional" type of analysis. In chromosome regions with extra or missing DNA -- indicating too many or too few copies of key genes -- the algorithm looks at how long the region is, how wide or "thick" it is, and how frequently it turns up in cancer tissue.

The Genome-Topography-Scan algorithm, as it is called, can help investigators prioritize their search for cancer-related genes, Chin says, and will be refined and improved as research continues. "By pointing to genes with a high probability of being involved in cancer, the technique can speed the process by which new cancer genes are identified and therapies are developed to counter them," she states.

Source: Dana-Farber Cancer Institute