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Study suggests brain tumors need treatment with multiple 'targeted' drugs

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Researchers at Dana-Farber Cancer Institute have shown that several, rather than just one, cell-growth switches are simultaneously overactive in many brain tumors and other solid tumors, explaining why treatment with just a single "targeted" switch-blocking drug often yields disappointing results.

The laboratory finding argues for quickly moving to clinical trials that combine three or more such targeted drugs for such cancers to shut down all the malfunctioning growth switches, according to the team led by Ronald DePinho, MD, director of the Center for Applied Cancer Science at the Dana-Farber. Their report is being posted online on Sept. 13 by the journal *Science* and will appear in a forthcoming print issue.

The switches are formed by molecules called receptor tyrosine kinases (RTKs) that often are mutated and hyperactive in cancer cells. Since a number of kinase-blocking drugs are already available -- Gleevec and Tarceva are two of the best-known -- the researchers said clinical trials of combinations of the compounds should be planned quickly.

"This is a transformative finding that will motivate clinicians and our pharmaceutical colleagues to design clinical trials with regimens using several inhibitors," said DePinho. He noted that in the laboratory study using cancer cell lines and fresh specimens of brain tumors, three or more kinase inhibitors were needed to quell the abnormal cell-growth signals.

The study focused on glioblastoma multiforme (GBM), an aggressive brain tumor that is nearly always fatal. The scientists also found similar patterns of multiply activated RTKs in other common cancers of the pancreas and lung.

Jayne Stommel, PhD, lead author of the report and a post-doctoral fellow in the DePinho lab, undertook a survey of molecular RTK "signaling pathways" in GBM cells to find the sources of abnormal growth.

RTKs are located on the surface of both normal and cancerous cells and receive signals from the cells' environment. Many of the signals are chemical "growth factors" directing the cell to divide and grow. Signals received by the RTKs are transmitted to the cell's nucleus via a pathway called PI3K, which often behaves abnormally in cancer cells.

At least 54 RTKs have been identified, and some, such as epidermal growth factor receptor (EGFR) have been implicated in glioblastomas. However, drugs that block EGFR have had limited success in delaying the progression of these and other virulent tumors. "Typically one elicits a positive initial response, but rarely durable cures," said DePinho, who is also a professor of medicine at Harvard Medical School. "Overall, the record of receptor tyrosine kinases inhibitors in these brain tumors has been somewhat disappointing."

Perhaps the problem was that other kinase pathways were also sending abnormal growth signals, acting as a redundant or backup source of growth simulation. "No one had looked to see how many receptor tyrosine kinases are activated at the same time in these cells," said Stommel.

The researchers tested 20 glioblastoma cell lines using an antibody array technique that measured the activation of 45 different RTKs at one time.

In 19 of the 20 cell lines, three or more RTKs were activated at the same time, sending abnormal growth signals in triplicate to the nucleus. Moving from cell lines to fresh cells, the researchers saw the same multiple-RTK activity when they studied tumor samples from newly diagnosed patients.

The kinase inhibitor imatinib (Gleevec) had little effect on the errant signaling pathways when applied to the brain tumor cells. But when imatinib was given in combination with two other kinase inhibitors, erlotinib (Tarceva) and SU11274, traffic in the PI3K signaling pathway was eliminated, and the cancer cells died.

The study's findings "provide a rational explanation for the feeble clinical responses" when RTK inhibitors are given singly to patients with solid tumors, the investigators wrote, and suggest that combination therapy should yield better results.

In addition, patients' tumors can be profiled to identify which among the many RTK switches are activated, so that tailored therapy with the appropriate combination of inhibitors can be prescribed.

"This study provides proof of concept for the eventual implementation of a 'personalized' therapeutic paradigm in human cancer," the researchers concluded.

Source: Dana-Farber Cancer Institute