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Gene vital to brain's stem cells implicated in deadly brain cancer

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Researchers from Columbia University Medical Center's Herbert Irving Comprehensive Cancer Center have identified a protein that activates brain stem cells to make new neurons - but that may be hijacked later in life to cause brain cancer in humans. The protein called Huwe1 normally functions to eliminate other unnecessary proteins and was found to act as a tumor suppressor in brain cancer.

These findings, published in the August 18 issue of *Developmental Cell*, were co-led by Antonio Iavarone, M.D., associate professor of neurology and pathology & cell biology and Anna Lasorella, M.D., assistant professor of pediatrics and pathology & cell biology, both of Columbia's Institute for Cancer Genetics at the Herbert Irving Comprehensive Cancer Center.

"By identifying the normal function of Huwe1, we were able to learn that deregulation of Huwe1 function is involved in tumor development," say Dr. Iavarone.

"This demonstrates that a gene's basic function must be understood before we can learn how it also plays a role in the development of cancer," says Dr. Lasorella.

During normal brain development, neural stem cells grow and divide rapidly before developing into neurons. To successfully change into neurons, they must remove all proteins that keep the cells in an immature, stem cell state. To understand how brain tumors develop, Drs.

Iavarone's and Lasorella's teams decided that they needed to understand the development of normal neural stem cells. Their research demonstrated that Huwe1 is responsible for "crowd control" for the mechanism that regulates the stem cell mass in the developing brain - effectively weeding out unnecessary stem cell-specific proteins - and promoting neurogenesis. Without Huwe1, Dr. Lasorella discovered that in mice, too few mature neurons form in the brain, resulting in the brain failing to properly develop.

Because the stem cells and cancer cells share the capacity for rapid proliferation, but cancer cells have lost crowd control, Dr. Iavarone then looked for signs of Huwe1 alterations in human brain tumors. Compared to normal brain tissue, he found that Huwe1 activity in tumors was significantly lower than in normal brain tissue.

"The loss of Huwe1 may be an important factor in the development of brain cancer, suggesting that Huwe1 protein function may be used for new therapeutic targets to fight deadly brain cancer," says Dr. Lasorella.

"Our next step will be to analyze the structural changes in Huwe1, and research ways to restore this gene in brain tumor patients," says Dr. Iavarone. "In mice, giving Huwe1 back blocks the ability of normal stem cells to proliferate and develop tumors. We are hopeful that if we can restore Huwe1 activity in brain tumor cells resulting from Huwe1 deletion, then we can stop the tumor growth."

Considering the relevance of the new findings, the paper has been selected for feature on the cover of this Aug. 18 issue of *Developmental Cell*. The coverage image (available upon request by emailing eas2125@columbia.edu) shows the alterations of neural cells in the mouse brain carrying inactivation of Huwe1 with the superimposed molecular network responsible for those alterations. The network was assembled by the lab of research team member Andrea Califano, Ph.D.,

a computational biologist at Columbia University Medical Center's Herbert Irving Comprehensive Cancer Center. The Califano lab developed computational algorithms to dissect transcriptional and post-transcriptional interaction that helped the team analyze the data - pinpointing the role of Huwe1. Dr. Califano is professor of biomedical informatics and founding director of Columbia's new Systems Biology Initiative.

Brain tumors are among the most devastating cancers for both children and adults.

According to the American Brain Tumor Association, brain cancer is the leading cause of cancer-related death in patients younger than age 35. Approximately 17,000 people in the United States are diagnosed with brain cancer each year and nearly 13,000 die of the disease. The annual incidence of primary brain cancer in children is about 3 per 100,000.

Brain tumors do not discriminate. Primary brain tumors - those that begin in the brain and tend to stay in the brain - occur in people of all ages, but they are statistically more frequent in children and older adults. Metastatic brain tumors - those that begin as a cancer elsewhere in the body and spread to the brain - are more common in adults than in children.

Brain tumors are the most common of the solid tumors in children, and the leading cause of death from solid tumors. Brain tumors are the second leading cause of cancer-related deaths in children under the age of 20. Leukemia remains the first.

There are few effective treatments for brain tumors, which are typically very aggressive -necessitating high doses of chemotherapy, which may result in neuro-deficiencies and learning disabilities in patients.

Source: Columbia University Medical Center (news : web)