Discovery of pathway for deadly cancer could lead to better diagnosis, treatment

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(Medical Xpress)—University of Florida Health researchers have discovered a molecular pathway involved in the deadly spread of the most lethal kind of brain cancer.

Their findings, which appear in the advanced online edition of *EMBO Molecular Medicine*, may help physicians make better decisions about treatment and help researchers pinpoint a target for therapeutic drugs in about half of all patients diagnosed with the form known as glioblastoma.

The National Cancer Institute estimates that 22,910 adults—12,630 men and 10,280 women—were diagnosed with brain and other nervous system tumors in 2012. It also estimates that more than half of these diagnoses will result in death.

Florian Siebzehnrubl, a UF research assistant professor of neurosurgery, collaborated on the research with colleagues from the department of neuroscience, the department of pathology, immunology and laboratory medicine and the UF Health Cancer Center as well as researchers from the University of Bonn, Germany and University Hospital Freiburg, Germany.

"Glioblastoma is the worst type of brain cancer, and also the most common brain cancer in adults," said Siebzehnrubl, a professor in UF's Evelyn F. & William L. McKnight Brain Institute. "There is no cure and the prognosis is poor, mainly because the cancer cells can quickly

infiltrate the entire brain."

These cells also resist chemotherapy, so even if surgery and irradiation eradicate the initial tumor, patients often suffer a recurrence of cancer soon after.

The researchers have found a molecular pathway, called the ZEB1 pathway, that, when present, causes cells to leave the initial tumor site, generates resistance to chemotherapy in these cells and generates new tumors away from the initial site.

"ZEB1 is known to be important in a number of cancers, functioning at the level of cancer stem cells, but there has been little work on this transcription factor in brain cancer," said David Sandak, vice president of Accelerate Brain Cancer Cure. "We are excited about the finding as it integrates a single regulatory pathway with multiple oncogenic mechanisms and provides promise for a new therapeutic target for glioma."

In patients who have this pathway, the course of the illness is much worse than in those where the pathway is not seen, Siebzehnrubl said. These patients get sick very quickly, don't respond to chemotherapy and die sooner than those who lack the pathway.

The key regulator appears to be a protein called ZEB1 that binds to specific DNA sequences to control the flow of genetic information that drives this pathway. This particular kind of protein does not a have a specific site where therapeutic drugs can bind, so the researchers must look elsewhere to see if they can target a molecule that activates the pathway farther upstream.

"This gives us an idea of what we can do to target these lethal cells," Siebzehnrubl said.

The laboratory's next steps will be to examine what else might be regulating these tumor cells, since this pathway occurs in only half of patients with glioblastoma.

"We also want to look at what is going on in patients where this pathway is not active," Siebzehnrubl said.

More information: onlinelibrary.wiley.com/doi/10 … m.201302827/abstract

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