Iron key to brain tumor drug delivery

June 2 2011

Brain cancer therapy may be more effective if the expression of an iron-storing protein is decreased to enhance the action of therapeutic drugs on brain cancer cells, according to Penn State College of Medicine researchers.

Malignant glioblastoma multiforme is a deadly brain tumor for which no long-term effective cure exists. Because drugs in the blood do not pass from the blood vessels to the brain, effective amounts of chemotherapy drugs do not reach the tumor. Increasing dosages damage normal brain tissue and cause significant neurological damage. These dosages also would likely be harmful to other organs in the body. However, by increasing the sensitivity of the cancer cells to drugs, the effectiveness of treatment can be increased.

"About half of all brain tumors are resistant to chemotherapy and new therapeutic strategies are urgently needed to treat this cancer," said James Connor, Ph.D., Distinguished Professor and vice-chairman of neurosurgery.

Connor and his graduate student Xiaoli Liu took advantage of the high iron requirements of the brain cancer cells to target ferritin, a protein that stores iron in all cells.

"High levels of iron are required in cancer cells to meet the energy requirements associated with their rapid growth," Connor said. "In addition, iron is essential for general cell health."

Working with Achuthamangalam Madhankumar, Ph.D., assistant professor of neurosurgery, the researchers used liposomes -- tiny lipid containers -- to deliver a fragment of RNA called interference or siRNA, to tumor cells. The siRNA targets the molecular machinery of the cell so that the protein cannot be made -- a process known as downregulation. By targeting and turning off ferritin in cancer cells, the protective function of H-ferritin disappears and the sensitivity to chemotherapy increases.

Using ferritin siRNA, the protein level decreases by 80 percent within 48 hours providing a window of opportunity for enhanced sensitivity to the chemotherapeutic agent. The researchers studied whether silencing ferritin would lower the effective dosage of BCNU, a chemotherapy drug used in brain tumor treatment and one of the few approved for brain cancer. While BCNU is effective, it has serious side effects limiting its use.

The use of siRNA reduces the amount of BCNU needed for tumor suppression by more than half in mice, according to the researchers, who published their findings in the journal *Cancer Research*.

"Our results further indicate that a nanoliposomal delivery mechanism can increase the efficacy of siRNA and optimize the amount of siRNA delivered," Connor said. "By silencing the ferritin gene, tumor sensitivity to chemotoxins was increased. The results from this project are a promising initial step toward the development of siRNA gene therapy involving ferritin for the treatment of multiple tumor types."

Provided by Pennsylvania State University