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Antibody targeting of glioblastoma shows promise in preclinical tests

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Cancer researchers at Georgetown University's Lombardi Comprehensive Cancer Center have successfully tested a small, engineered antibody they say shuts down growth of human glioblastoma tumors in cell and animal studies. Glioblastoma is the deadliest of brain cancers; there is no effective treatment.

In the current online issue of the journal Oncogene, the researchers demonstrate how this antibody latches onto a receptor that studs the outside of glioblastoma cells, preventing a growth factor protein from binding to it and activating growth pathways in the tumors.

"We desperately need new treatments for glioblastoma, and these findings have given us hope that a new approach may be possible," says the study's lead investigator, Anton Wellstein, MD, PhD, a professor of oncology and pharmacology at Lombardi.

He adds that ALK receptors and the protein that binds to it, the growth factor pleiotrophin (PTN), are both also over-expressed in other difficult-to-treat cancers, such as melanoma and pancreatic tumors. "We have found that PTN drives metastasis of those cancers, suggesting that antibody treatment may be additionally useful in those cancers," Wellstein says.

Researchers at Lombardi/Georgetown University Medical Center have been working on this line of research since the mid 1980s, and the institution holds a patent on the "target" of the novel antibody- a region

on the ALK receptor. The patent also covers potential therapies. Before Wellstein joined Lombardi in 1989, he worked at the National Cancer Institute with other investigators hunting for growth factors that are secreted by cancer cells, and they eventually reported on PTN in 1992. He and his colleagues spent the next years finding PTN's receptor, which is ALK. They have since characterized the relationship between PTN and ALK, reporting in this study that many brain cancers overexpress PTN and ALK very similar to the developing brain. "When the brain is developing, it needs to constantly remodel itself," he says. "Glioblastoma appears to be another example of cancer that develops when embryonic genes are upregulated. As a result, brain tumor cells are extremely motile and can invade other parts of the brain very quickly."

In this latest research, Wellstein and his colleagues searched public databases, at the National Library of Medicine, to see if other studies that collected and analyzed glioblastoma and other brain tumor tissues also recorded expression of PTN and ALK, as well as genes along this pathway. "We found that they are significantly up regulated," he says. They then assessed whether that activity mattered to the outcome of patients with brain tumors. "A lot of pathways that are activated in cancer are passengers, in a sense. They don't drive cancer. But in the case of PTN and ALK, the expression data suggest that these are drivers - patients with increased expression of these genes had significantly poorer outcomes in an analysis of different, independent studies."

Wellstein had also been working on a method to shut off the pathway. Several years ago, GUMC investigators found the "sweet spot" on ALK where PTN binds, which Wellstein says was a major discovery. "You can have hundreds of different areas on a receptor protein where its ligand could theoretically bind. We found just the right one."

They collaborated with ESBAtech in Switzerland who created a small single-chain antibody fragment in yeast that would itself bind to the

sweet spot, blocking ALK's interaction with PTN. In the present study, the researchers successfully tested the antibody in human glioblastoma cells, and also showed that in mice implanted with human glioblastoma, the antibody prevented tumors from growing. For example untreated tumors grew to an average size of 350 cubic millimeters after three weeks, but treated tumors did not grow beyond their initial 25 cubic millimeters.

Wellstein says a phase I clinical trial of the therapy is in the discussion stage, but much remains to be worked out. For example, it is uncertain how the antibody should be administered. Because it may not pass through the blood-brain barrier, it could possibly be delivered through a viral vector, or administered following brain surgery.

While antibodies are used to treat a variety of cancers, such as Herceptin for breast cancer, no antibody treatment has yet been approved for brain diseases, although some are being tested, Wellstein says.

"Developing this approach to treating glioblastoma is very exciting," he says.

Source: Georgetown University Medical Center (news : web)