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Swell effect on glioma

By Michael J. Haas, Senior Writer

Gliomas, unlike most other tumor types, grow and expand by killing off surrounding tissue, causing neurodegeneration and edema. Chemotherapy and radiotherapy attack the tumor itself, but do not address these two other effects of the cancer. A paper in *Nature Medicine* suggests that neurodegeneration and edema can be alleviated by hitting one target—the glutamate transporter xCT—making selective inhibition of xCT a potentially useful adjunct to glioma treatments.

For a nearly a decade it has been known that the neurodegeneration associated with gliomas results from their release of excess glutamate triggered by xCT overexpression.[1,2] The *Nature Medicine* paper now reports that the induced neurodegeneration is a significant—if not the exclusive—contributor to brain edema.

The study, from researchers at the **Swiss Federal Institute of Technology Zurich**, the **University of Zurich**, **The Netherlands Cancer Institute**, the **University of Erlangen-Nuremberg** (FAU) and the **University of Cologne**, showed that selective inhibition of xCT reduced neurodegeneration and edema and that it conferred a survival benefit despite having no effect on tumor proliferation.[3]

The research team was led by Ilker Eyüpoğlu, neurosurgeon and principal investigator at FAU. According to Eyüpoğlu, the prevailing theory has been that glioma-induced brain edema results from leaky tumor blood vessels and disruption of the blood-brain barrier during tumor angiogenesis. Both processes allow entry of fluids that do not ordinarily cross into the brain.

"In our work we provide evidence that glutamate secretion and cytotoxic events—neuronal cell death—contribute to the edema formation," he told *SciBX*.

xCT role

xCT is a transmembrane protein expressed on neurons, astrocytes and glioma cells. It mediates cellular secretion of glutamate in exchange for cystine. Cystine is required for the synthesis of the antioxidant glutathione (GSH), which protects cells from free radicals and other oxidizing toxins.

The role of xCT in glioma-induced neurodegeneration was first elucidated in 1999 by researchers from the **University of Alabama at Birmingham** (UAB) and **Johns Hopkins University**, led by Harald Sontheimer, professor of neurobiology at UAB.[1,2] Those studies showed that gliomas overexpress xCT and release excessive amounts of extracellular glutamate, killing the surrounding neural tissue through excitotoxicity. They also showed that overexpression of xCT increased glioma uptake of cystine, resulting in higher GSH levels that increased the tumor's resistance to radio- and chemotherapies.

Sontheimer and colleagues identified the xCT inhibitor, *S*-4-carboxyphenylglycine (*S*-4-CPG), used in the recent *Nature Medicine* paper.

According to Eyüpoğlu, those earlier studies with *S*-4-CPG focused on how reducing GSH within the glioma affected tumor size, and they used high concentrations of the compound (250–500 µM).

"In our paper, we provide data that *S*-4-CPG is already potent enough to inhibit glutamate secretion below 100 µM without affecting proliferation," he said, which allowed the team to study the effects of inhibiting glutamate secretion in the absence of changes in tumor size.

To investigate those effects, the team used short interfering RNA and *S*-4-CPG to confirm that blocking xCT in glioma cells and human brain tissue samples reduced glutamate secretion and subsequent neuronal damage.

Next, the team observed that rats injected with xCT-silenced gliomas had delayed neurodegeneration and prolonged survival compared to control rats injected with untreated gliomas.

Then the team showed that low doses of *S*-4-CPG delayed onset of neurodegeneration, reduced edema and prolonged survival in control rats, even though tumor volume remained unchanged.

Eyüpoğlu noted that previous studies demonstrated xCT is "dispensable for normal development, cell proliferation and health" in mammals.[4,5] Thus, he said, selective targeting of xCT could treat both edema and neurodegeneration in glioma patients without significant side effects.

UAB's Sontheimer told *SciBX* that his own research teams have not studied glioma-induced edema, "so this aspect of the *Nature Medicine* paper may well be new." He did note that edema can also result from tumor necrosis.

Eyüpoğlu said his team is exploring the extent to which glioma-induced neurodegeneration contributes to brain edema, relative to other possible factors such as tumor growth and necrosis.

Adjuvant therapy

Companies told *SciBX* that xCT inhibitors might work as adjuncts to existing chemotherapies, but they expect that *S*-4-CPG may not be the optimal candidate.

Andrew Mazar, CSO of **Attenuon LLC**, said that "to see something that reduces both glioma-related neurodegeneration and edema *in vivo* is a significant advance." He said that the 30% increase in survival observed with low doses of *S*-4-CPG is also noteworthy—especially in the absence of any effect on tumor size.

"How or whether neurodegeneration and edema contribute to mortality has been hard to tease apart from the tumor's contribution," Mazar said. "But these results imply that neurodegeneration leads to lower survival rates."

Thus, he said, an xCT inhibitor could be useful in combination with a drug that both increases survival and shrinks tumors, such as Avastin bevacizumab, an antibody to VEGF from **Genentech Inc.** and **Roche** that is marketed for colorectal cancer and non–small cell lung cancer (NSCLC).

Glioma is typically treated with surgery followed by chemotherapy. However, companies are pursuing the development of combination therapies. For example, the combination of Avastin and Camptosar irinotecan, a topoisomerase inhibitor from **Pfizer Inc.**, is in a Phase III trial to treat recurrent glioblastoma multiforme.[6]

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>
> ***—Alistair Stewart, Allon Therapeutics Inc.***

Mazar thinks that "Avastin plus irinotecan is on the way to becoming the new standard of care."

Attenuon is developing ATN-161, a five-residue peptide derived from fibronectin that targets integrin $\alpha_5\beta_1$ and integrin $\alpha_v\beta_3$. Last year, the company halted a Phase II trial of an i.v. formulation of the compound in intracranial malignant glioma to reformulate it for subcutaneous injection. Attenuon expects to reenter the clinic within 18 months.

Alistair Stewart, director of corporate development at **Allon Therapeutics Inc.**, said the inability of *S*-4-CPG to cross the blood-brain barrier presented a significant hurdle—but not an insurmountable obstacle—to its use in treating neurodegenerative indications.

"Small lipophilic molecules will cross the blood-brain barrier," but molecules that are too large or too polar, such as *S*-4-CPG, will be excluded from the brain, he said.

Allon's AL-309, a nine-amino-acid peptide, is in preclinical studies as a neuroprotectant to treat Alzheimer's disease and amyotrophic lateral sclerosis (ALS).

Stewart suggested that one way around this barrier might be to deliver *S*-4-CPG during surgery, in a manner similar to Gliadel Wafer from MGI Pharma Inc., a subsidiary of **Eisai Co. Ltd.** This carmustine implant is a chemotherapeutic agent implanted in the brain upon the surgical removal of gliomas.

Another potential solution is to use a different xCT inhibitor, such as sulfasalazine, a generic that is marketed to treat Crohn's disease. In 2005, Sontheimer and colleagues identified this molecule as an xCT inhibitor,[7] and he and UAB are planning a Phase I trial of the compound as an adjuvant to treat brain cancer.

"If the UAB group has some positive data in their clinical study, someone will pick up on this and try to reposition sulfasalazine," said Mazar.

Beyond glioma

Allon's Stewart said he also wants to see whether targeting xCT "has an impact on neuronal survival and edema in other indications." If so, he said, the *Nature Medicine* findings could have implications for other neurodegenerative indications such as Alzheimer's disease (AD), stroke and traumatic brain injury.

"This broader application may be needed because glioblastoma is a small market relative to other cancers," he said. "I would be looking to demonstrate the importance of xCT in other conditions, in order to maximize the potential of new drugs against this target."

Meanwhile, the next steps for Eyüpoğlu's team include studying whether lower levels of cystine and GSH in xCT-silenced tumors indeed make brain tumors more susceptible to chemotherapy. Eyüpoğlu said the findings reported in *Nature Medicine* are not patented.

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COMPANIES AND INSTITUTIONS MENTIONED

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