

Researchers discover mechanism in brain cancer responsible for neuron death

November 3 2011

Researchers from Virginia Commonwealth University Massey Cancer Center and the VCU Institute of Molecular Medicine have discovered a mechanism by which glioblastoma multiforme (GBM), the most common form of brain cancer, promotes the loss of function or death of neurons, a process known as neurodegeneration.

The findings could lead to new therapies that suppress neurodegeneration caused by GBM and, potentially, a variety of other [neurodegenerative diseases](#).

The study, recently published in the journal *Cancer Research*, was led by Paul B. Fisher, M.Ph., Ph.D., Thelma Newmeyer Corman Endowed Chair in Oncology Research and co-program leader of Cancer Molecular Genetics at VCU Massey, professor and chair of the Department of Human and [Molecular Genetics](#) in the VCU School of Medicine and director of the VCU Institute of [Molecular Medicine](#). The research revealed that the oncogene (a gene with the ability to cause cancer) astrocyte elevated gene (AEG)-1 promotes neurodegeneration by increasing glutamate toxicity to neurons. Glutamates play an important role in the transmission of signals between neurons and are important for [learning and memory](#). On the other hand, glutamates can build up in the synapses, or spaces between neurons, and lead to [neuron death](#) through overstimulation, a process known as excitotoxicity.

This study is the first of its kind in that it provides a direct mechanistic link between GBM, neurodegeneration and glutamate transport and

explains a process by which GBM, through expression of the AEG-1 oncogene, can provoke the death of neurons. AEG-1 was originally cloned in Fisher's laboratory and is overexpressed in more than 90 percent of all [brain tumors](#).

"Gliomas are the most common brain tumor and are the second-leading cause of [cancer death](#) among adults 20 to 39 years old," says Fisher. "In highlighting the importance of AEG-1 in [brain cancer](#) development, progression and neurodegeneration, we have identified a new target for inhibiting both of these processes through therapeutic intervention."

Fisher's team demonstrated that AEG-1 negatively correlates with the expression of excitatory amino acid transporter 2 (EEAT2), the primary glutamate transporter in glial cells (which surround neurons and provide support for them and insulation between them) found in the brain and spinal cord. EEAT2 is essential for maintaining appropriate levels of glutamate in synapses and failure to regulate the glutamate level results in excitotoxicity. The researchers also showed that AEG-1 inhibits expression of EEAT2 during transcription, the process by which genes are expressed in the nucleus of cells, through several mechanisms that lead to excitotoxicity due to excessive glutamate. This relationship between AEG-1 expression and neurotoxicity was demonstrated using GBM patient samples.

"Understanding glutamate transport is very important for a variety of neurodegenerative diseases, including glioma-induced neurodegeneration, amyotrophic lateral sclerosis (ALS), Huntington's disease, Alzheimer's, epilepsy, brain ischemia and more," said Fisher. "Our lab was the first to clone the EEAT2 promoter, and we plan to use it to screen for small molecules, or drugs, capable of regulating extracellular glutamate transport and preventing neurodegeneration."

Moving forward, Fisher and his team will work to construct advanced

animal models to further study the role of AEG-1 and glutamate in brain development and function. Once created, these models will also help test the drugs identified in the small molecule screening process. The ultimate goal is to use this research to develop treatments for neurodegeneration caused by GBM and other diseases.

More information: Cancer Res August 18, 2011 canres.0782.2011; Published Online; August 18, 2011; [doi: 10.1158/0008-5472.CAN-11-0782](https://doi.org/10.1158/0008-5472.CAN-11-0782)

Provided by Virginia Commonwealth University

Citation: Researchers discover mechanism in brain cancer responsible for neuron death (2011, November 3) retrieved 19 September 2024 from <https://medicalxpress.com/news/2011-11-mechanism-brain-cancer-responsible-neuron.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.