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From brain tumors to memory: A very multifunctional protein

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Everything is connected, especially in the brain. A protein called BAI1, involved in limiting the growth of brain tumors, is also critical for spatial learning and memory, researchers have discovered.

Mice missing BAI1 have trouble learning and remembering where they have been. Because of the loss of BAI1, their neurons have changes in how they respond to electrical stimulation and subtle alterations in parts of the cell needed for information processing.

The findings may have implications for developing treatments for neurological diseases, because BAI1 is part of a protein regulatory network neuroscientists think is connected with autism spectrum disorders.

The results are scheduled for online publication March 9 in *Journal of Clinical Investigation*.

Erwin Van Meir, PhD, and his colleagues at Winship Cancer Institute of Emory University have been studying BAI1 (brain-specific angiogenesis inhibitor 1) for several years. Part of the BAI1 protein can stop the growth of new blood vessels, which growing cancers need. Normally highly active in the brain, the BAI1 gene is lost or silenced in brain tumors, suggesting that it acts as a tumor suppressor.

The researchers were surprised to find that the brains of mice lacking the BAI1 gene looked normal anatomically. They didn't develop tumors

any faster than normal, and they didn't have any alterations in their blood vessels, which the researchers had anticipated based on BAI1's role in regulating blood vessel growth. What they did have was problems with spatial memory.

"Because BAI1 is very active in the hippocampus, a region of the brain critical for learning and memory, we decided to look at the performance of the knockout mice on a memory task dependent on the hippocampus," Van Meir says.

The mutant mice had difficulty learning and remembering the location of a hidden platform in a water maze, which ordinary mice accomplish with ease. However, when the platform is not hidden, the mutant mice do fine in the test, indicating that their vision and motor function is not disrupted.

Van Meir and research associate Dan Zhu, PhD teamed up with Yoland Smith, PhD and Donald Rainnie, PhD and their colleagues at Yerkes National Primate Research Center to examine the neurons lacking BAI1 more closely. The scientists found that neurons lacking BAI1 show changes in long-term potentiation (LTP) and long-term depression (LTD): how the cells respond to patterns of incoming electrical signals.

"Traditionally, LTP has been associated with learning," Rainnie says. "But what we're seeing in these mice is that the balance between LTP and LTD is upset, and that disturbance may lead to the problems in spatial memory acquisition."

Further probing the effects of removing BAI1 via electron microscopy, Smith and his co-workers found that the post-synaptic density is thinner in mutant neurons. The post-synaptic density is a specialized area full of proteins needed for communication between neurons, so changes in its structure or capacity may explain the aberrant electrical responses.

BAI1-mutant neurons have less of an important scaffolding protein that anchors the post-synaptic density called PSD-95. BAI1 seems to antagonize another protein, MDM-2, which usually degrades PSD-95. MDM2 is also a well-known regulator of "guardian of the genome" p53.

"The newfound ability of BAI1 to neutralize MDM2 is intriguing," Van Meir says. "This function for BAI1 may have implications for cancer biology, since MDM2 can function as an oncogene by degrading important tumor suppressors like p53."

Several genes linked with autism spectrum disorders converge on regulating PSD-95, in connection with pruning or remodeling synapses, a process that appears to be altered in those disorders.

In addition to the functions in the brain described here, BAI1 is also thought to have functions in muscle regeneration and in the engulfment and removal of dying cells. Still other properties of this brain protein may be waiting to be discovered, since BAI1 is an "orphan" G-protein coupled receptor or GPCR, for which no ligand has been identified (yet).

GPCRs are the targets of dozens of drugs and are involved in vision, smell and responses to many hormones and neurotransmitters, but exactly what triggers BAI1's G-protein signals remains unknown, Van Meir says.

More information: Multiple autism-linked genes mediate synapse elimination via proteasomal degradation of a synaptic scaffold PSD-95, www.ncbi.nlm.nih.gov/pmc/articles/PMC3530171/

Provided by Emory University