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Neural precursor cells induce cell death in certain brain tumors

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Neural precursor cells (NPC) in the young brain suppress certain brain tumors such as high-grade gliomas, especially glioblastoma (GBM), which are among the most common and most aggressive tumors. Now researchers of the Max Delbrück Center for Molecular Medicine (MDC) Berlin-Buch and Charité – Universitätsmedizin Berlin have deciphered the underlying mechanism of action with which neural precursor cells protect the young brain against these tumors. They found that the NPC release substances that activate TRPV1 ion channels in the tumor cells and subsequently induce the tumor cells to undergo stress-induced cell-death.

Despite surgery, radiation or chemotherapy or even a combination of all three treatment options, there is currently no cure for glioblastoma. In an earlier study the research group led by Professor Helmut Kettenmann (MDC) showed that neural precursor cells migrate to the glioblastoma cells and attack them. The neural precursor cells release a protein belonging to the family of BMP proteins (bone morphogenetic protein) that directly attacks the tumor stem cells. The current consensus of researchers is that tumor stem cells are the actual cause for continuous tumor self-renewal.

Kristin Stock, Jitender Kumar, Professor Kettenmann (all MDC), Dr. Michael Synowitz (MDC and Charité), Professor Rainer Glass (Munich University Hospitals, formerly MDC) and Professor Vincenzo Di Marzo (Istituto di Chimica Biomolecolare Pozzuoli, Naples, Italy) now report a new mechanism of action of NPC in astrocytomas. Like glioblastomas,

astrocytomas are brain tumors that belong to the family of gliomas. Gliomas are most common in older people and are almost invariably fatal.

As the MDC researchers showed, the NPC also migrate to the astrocytomas. There they do not secrete proteins, but rather release fatty-acid substances (endovanilloids) which are harmful to the cancer cells. However, in order to exert their lethal effect, the endovanilloids need the aid of a specific ion channel, the TRPV1 channel (transient receptor potential vanilloid type 1), also called the vanilloid receptor 1. TRPV1 is already known to researchers as a transducer of painful stimuli. It has, among other things, a binding site for capsaicin, the irritant of hot chili peppers, and is responsible for the hot sensation after eating them. Clinical trials are currently underway to develop new pain treatments by blocking or desensitizing this ion channel.

MDC researchers describe an additional role of the TRPV1 ion channel

In contrast to its use in pain management, this ion channel, which is located on the surface of glioblastoma cells and is much more abundant there than on normal glial cells, must be activated to trigger cell death in gliomas. The activated ion channel mediates stress-induced cell-death in tumor cells. If however TRPV1 is downregulated or blocked, the glioma cells are not destroyed. The MDC researchers are thus the first to identify neural precursor cells as the source of fatty acids that induce tumor cell death and to describe the role of the TRPV1 ion channel in the fight against gliomas.

However, the activity of neural precursor cells in the brain and thus of the body's own protective mechanism against gliomas diminishes with increasing age. This could explain why these tumors usually develop in

older adults and not in children and young people. How can the natural protection of neural precursor cells be harnessed for older brains? According to the researchers, neural precursor cell therapy is not a solution. The benefit this obviously brings in the treatment of young people can have the opposite effect in older adults and may trigger brain tumors.

One possible treatment would be to use drugs to activate the TRPV1 channels. In mice, the group showed that a synthetic substance (arvanil), which is similar to capsaicin, reduced tumor growth. However, this substance has not yet been approved as a drug because the adverse side effects for humans are too severe. It is only used in basic research on mice, which tolerate the substance well. "In principle, however," the researchers suggest, "synthetic vanilloid compounds may have clinical potential for brain tumor treatment."

More information: Neural precursor cells induce cell-death of high-grade astrocytomas via stimulation of TRPV1, *Nature Medicine* http://dx.doi.org/10.1038/nm.2827

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