Why don't brain tumors respond to medication?

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Malignant brain tumors often fail to respond to promising new medication. Researchers in Heidelberg have discovered a mechanism and a tumor marker for the development of this resistance. A "death receptor" can possibly provide information as to how great the chances of success are for chemotherapy. At the same time, it offers a new approach for promising brain tumor therapy.

Dr. Wolf Müller, senior consultant in the Neuropathology Department at the Institute of Pathology of Heidelberg University Hospital, and his team were able to show that certain brain tumors (astrocytomas) can deactivate a crucial protein on their cell surface, the so-called death receptor. The medication docks onto this receptor and causes the cells to die. An intact "death receptor" can thus serve as a tumor marker for whether or not a therapy has a chance of success. The study was conducted with funding from the Tumor Center of Heidelberg/Mannheim and was published in the journal *Clinical Cancer Research*.

Primary brain tumors that develop from brain cells, in particular their most malignant variant the glioblastoma, have a very poor prognosis. Although various kinds of therapies are attempted, patients with a glioblastoma usually die within two years of diagnosis. The researchers are thus working at high speed to become more familiar with the biology of these tumors in order to develop more efficient treatment.

"Death receptor" can be switched on and off

The researchers in Heidelberg examined various primary brain tumors (astrocytomas, which also include glioblastomas) and discovered that the gene for the death receptor DR4 was switched off in up to 75 percent of cases by what is known as "promoter methylation". This means that methyl groups accumulate at the segment of the gene that is crucial for its activity (expression). The gene's information can thus no longer be read, the gene is silenced.

The death receptor DR4 is an attractive target for receptor-specific therapy. Fortunately, an already-existing drug, Mapatumumab, an antibody protein, binds directly to the receptor and can trigger the death of the cell. This drug is currently being tested in a number of clinical studies (Phase II) for other solid tumors, e.g. lung cancer.

New approach for a specific therapy for brain tumor cells

For gliomas, treatment with Mapatumumab appears to be particularly interesting as the death receptor is usually found only on tumor cells, not on other brain cells. Since glioma growth is especially invasive into brain tissue, surgical removal is impossible and chemotherapy is very difficult. Chemotherapy with Mapatumumab could reach all tumor cells and kill them while sparing healthy brain cells without receptors.

In cell culture trials, the researchers have already been successful in reversing methylation and making the "death receptors" functional again - tumor cells reacted to the drugs and died off. If gene expression was again suppressed, the cells became resistant again.

"Therapies that are capable to switch on specific individual genes by these manipulations do not yet exist. But being aware of the tumor markers can point the way for the development of new therapies whose

goal is gene manipulation," explained Dr. Wolf Müller. Targeted examinations of tumor tissue prior to therapy can now make it possible to identify patients with an intact death receptor. These patients have good conditions for benefiting from the promising therapy, while other patients would at least be spared the side effects of useless treatment.

More information: Epigenetic Silencing of Death Receptor 4 Mediates Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand Resistance in Gliomas. Agnes Elias, Markus D Siegelin, Albert Steinmüller, Andreas von Deimling, Ulrike Lass, Bernhard Korn, Wolf Mueller, *Clinical Cancer Research*, 2009, Epub ahead of print.

Source: University Hospital Heidelberg (news : web)