

# A circuitous route to therapy resistance

June 26 2013

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Gliomas are malignant brain tumors that arise from glial cells called astrocytes, found in the central nervous system. "In treating malignant gliomas, we currently combine radiotherapy with the anticancer drug temozolomide. However, in some patients, tumors rapidly become resistant to both treatment methods," says neurooncologist Professor Dr. Michael Platten, who leads a cooperation unit of the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) and the Department of Neurooncology of Heidelberg University Hospital. "We therefore urgently need new methods of treating these diseases more effectively."

Chemotherapy and radiotherapy damage the DNA of tumor cells. Normally these DNA defects automatically trigger the [cellular suicide](#) program known as apoptosis. However, tumor cells possess an efficient DNA repair system that they use to protect themselves from the consequences of therapy, thus evading cell death.

Key repair mechanisms in the cell can only work efficiently if a molecule called NAD<sup>+</sup> is present. When DNA repair is running at full throttle, as is the case during radiation therapy, NAD<sup>+</sup> supplies are quickly exhausted in a cancer cell, leading to DNA damage that goes unrepaired and ultimately cell death. Cancer researchers are therefore trying to use drugs to deprive cells of NAD<sup>+</sup> to prevent resistance to therapies. Substances that inhibit the enzyme which produces NAD<sup>+</sup> are already being tested in clinical trials.

However, cells can produce NAD<sup>+</sup> in a number of ways. They can

synthesize it directly, or use a substance called quinolinic acid, a metabolite of the protein building-block tryptophan, as an alternative source to produce NAD<sup>+</sup>. Michael Platten and his team had discovered that [malignant gliomas](#) contain large amounts of quinolinic acid. "We wanted to know whether gliomas might use this circuitous route in order to produce enough NAD<sup>+</sup> and thus escape therapy," says neuropathologist Felix Sahm, first author of the publication.

If direct NAD<sup>+</sup> production is blocked, malignant glioma cells, unlike normal astrocytes, increase production of QRPT. This enzyme breaks down quinolinic acid into NAD<sup>+</sup>. Therapies involving the anticancer drug temozolomide, radiation, or oxidative stress were found to lead to increased levels of QRPT in tumors. The higher the degree of malignancy of the gliomas that were investigated, the more QRPT they contained. Brain tumors that recurred after combined radiotherapy-chemotherapy had a poorer prognosis when the cancer cells produced high levels of quinolinic acid.

The researchers also discovered that the tumor cells are not capable of forming quinolinic acid on their own. Instead, the substance is produced by immune cells called microglia, which migrate in large quantities into gliomas. Microglia cells may constitute up to 50 percent of the total cell content of a glioma.

In these cases, only the tumor cells contain QRPT; healthy astrocytes do not. Hence only the tumor cells are capable of breaking down quinolinic acid into NAD<sup>+</sup>. "The malignant transformation of astrocytes appears to be linked to their ability to use quinolinic acid as an alternative source of NAD<sup>+</sup> and thus develop resistance against radiotherapy and chemotherapy," says Michael Platten. "A link between microglia and the malignancy of gliomas has been known for some time – now we may have found a possible cause. The key enzyme for the alternative NAD<sup>+</sup> supply is QRPT. An agent directed against this enzyme might help

suppress therapy resistance in brain cancer. This might enable us to achieve better outcomes in treating [malignant brain tumors](#) using existing methods."

**More information:** Felix Sahn, Iris Oezen, Christiane A. Opitz, Bernhard Radlwimme<sup>5</sup>, Andreas von Deimling, Tilman Ahrendt, Seray Adams, Helge B. Bode, Gilles J. Guillemin, Wolfgang Wick and Michael Platten: The Endogenous Tryptophan Metabolite and NAD<sup>+</sup> Precursor Quinolinic Acid Confers Resistance of Gliomas to Oxidative Stress. Cancer Research 2013, [DOI: 10.1158/0008-5472.CAN-12-3831](https://doi.org/10.1158/0008-5472.CAN-12-3831)

Provided by Helmholtz Association of German Research Centres

Citation: A circuitous route to therapy resistance (2013, June 26) retrieved 20 November 2023 from <https://medicalxpress.com/news/2013-06-circuitous-route-therapy-resistance.html>

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