

Combination therapy can prevent cytostatic resistance

November 26 2015



Researchers at Karolinska Institutet have found a new way of preventing resistance to cytostatics used in the treatment of cancers such as medulloblastoma, the most common form of malignant brain tumour in children. The promising results of this experimental study are based on a combination of the drug temozolomid and other extant drugs that inhibit

an enzyme instrumental in DNA repair in cancer cells.

The study, which is published in the journal *Nature Communications*, was conducted on human tumour cells and on mice, and offers hope of a much improved therapy for a severe form of cancer. This says the research team is particularly valuable for children, whose brains are still developing and who thus run the highest risk of injury from the radiotherapy often used against malignant brain tumours.

"Now that we've tested already available drugs, the published results enable us to move on to clinical trials relatively quickly, which is very good news indeed," says Dr Malin Wickström, one of the researchers behind the study.

The treatment of cancer often involves different forms of cytostatic drugs as well as surgery and radiotherapy. However, tumour cells develop strategies for resisting these drugs, most commonly to produce more of a particular protein or enzyme able to repair the DNA damage caused by the chemotherapy.

In the present experimental study, the researchers have sought means of inhibiting the DNA-repair enzyme MGMT (O6-methylguanine-DNA-methyltransferase), which plays a key part in cytostatic resistance. One finding was that a cell signal pathway called Wingless and its central signal molecule, beta-catenin, can regulate the production of MGMT in the tumour cell.

Common form of paediatric brain tumour

Blocking Wingless/beta-catenin also inhibits the MGMT enzyme, which in turn prevents cytostatic resistance. This was particularly the case for temozolomid, which is often used to treat medulloblastoma, the most common form of paediatric brain tumour.

"By combining temozolomid with Wingless inhibitors, we've been able to cancel out the resistance developed by the tumour, rendering it susceptible to the tumour-killing effect of temozolomid," says principal investigator and docent, Dr John Inge Johnsen. "We hope that the results will give rise to a new drug combination therapy and improve prospects for a very vulnerable patient group."

More information: Malin Wickström et al. Wnt/ β -catenin pathway regulates MGMT gene expression in cancer and inhibition of Wnt signalling prevents chemoresistance, *Nature Communications* (2015). DOI: [10.1038/ncomms9904](https://doi.org/10.1038/ncomms9904)

Provided by Karolinska Institutet

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