Combination of medications slows down brain tumours in children

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In collaboration with a number of American colleagues, researchers from Uppsala University have found an Achilles' heel for the most common form of malignant child brain tumours. By combining two kinds of medicines, it is possible to simultaneously attack the cancer cell's division and its reinforcement system, which is necessary in order for treatment to be sufficiently effective.

MYC is a protein that can bind to specific locations in the genome (DNA) inside the cell's nucleus and which thus controls the production of a number of important genes. MYC is often overly produced in aggressive cancer of the medulloblastoma type which is the most common form of malignant brain tumour that afflicts children. MYC proteins control cancer growth by first directing proteins that control the cell cycle to increase cell division and then increase the various reinforcement signals in the cancer cell which makes it even more dangerous. Although MYC proteins are involved in almost half of all types of cancer in humans, there are currently no effective medicines which, when used individually, can inhibit them in a direct way.

The research team, led from Uppsala University, first tested a drug that inhibits the protein CDK2, which in turn controls the cell cycle of dividing cancer cells. The drug was shown to slow down the cell cycle and also effectively inhibit MYC in brain cancer cells. However, it was only when the drug was used in combination with a BET inhibitor, a substance that prevents MYC from reinforcing other genes in the cell, that the effect was strong enough to really stop the cancer's growth. The two substances were tested in various model systems controlled by MYC proteins and direct on cultivated brain cancer cells from patients with abnormally high levels of MYC proteins.

"We saw that the substances used in the treatment were able to cross the blood brain barrier, which means they can actually make their way in and attack the tumour cells in the brain. The brain is enveloped by the blood brain barrier and normally it prevents unnecessary or potentially dangerous substances, including many types of medicines, from reaching the brain. Of course, a medicine must be able to make its way all the way to its target in the brain in order for it to be used effectively in the clinical treatment of these patients," says Fredrik Swartling, associate professor at the Department of Immunology, Genetics and Pathology at Uppsala University, who led the study.

The medicine that inhibits CDK2 is already being tested clinically for other types of cancer, but the BET inhibitor does not have sufficiently stable properties in the body which is necessary if it is to be used as a medicine. In the absence of a more stable BET inhibitor that can cross the blood brain barrier, it is not yet possible to test this combination on patients with medulloblastoma.

Nevertheless, the results, which have been published in the scientific journal *Oncogene*, show that this combination is very effective for the most serious types of brain tumours that have high levels of MYC.

More information: Sara Bolin et al. Combined BET bromodomain and CDK2 inhibition in MYC-driven medulloblastoma, *Oncogene* (2018). DOI: 10.1038/s41388-018-0135-1

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