Malignant brain tumours can be transformed into benign forms

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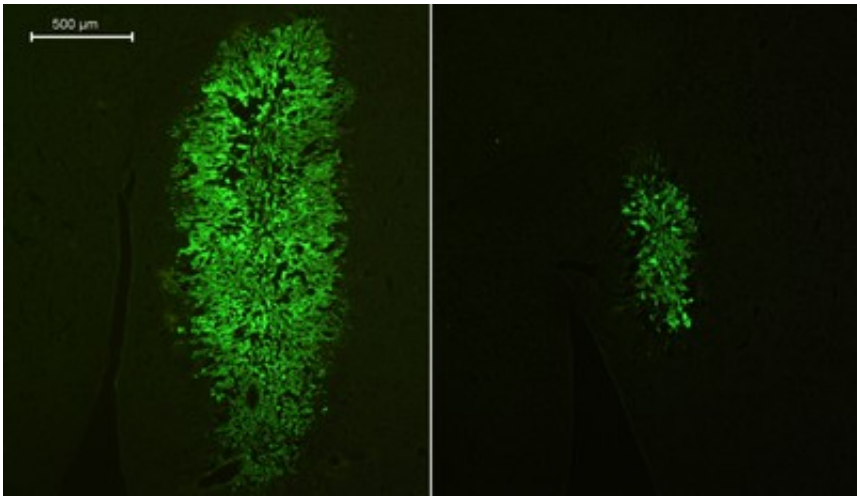

Left: Typical malignant glioma inside a mouse brain. Right: Glioma in the brain of another mouse, transformed into bening form. Credit: Nencki Institute

Cells of malignant brain tumours deceive our immune system so effectively that it starts working for them. But who lives by the sword, dies by the sword. Researchers from the Nencki Institute in Warsaw show how to deceive brain tumours and change malignant gliomas into benign forms.

The research team of Prof. Bo?ena Kami?ska from the Nencki Institute of Experimental Biology of the Polish Academy of Sciences in Warsaw developed – so far only in animal model – a method of converting malignant gliomas (brain tumours) into benign forms. Since the cells of

benign gliomas are subdued and sometimes even eliminated by the host's immune system, the prospects for survival of sick animals significantly increase. This novel research was funded by the Polish National Science Centre.

The nervous system, including the brain, is inhabited, besides neurons and glial cells, by microglial cells. They support the nervous cells but also have important protective functions, patrolling the surroundings with their extenses and eliminating damaged or unnecessary cells. As macrophages of our immune system they also fight foreign bacteria, viruses and tumorous cells. Unfortunately, sometimes the glia cells themselves become cancerous. This is how brain tumours called gliomas form. However, they are not uniform entity and could differ significantly with respect to their behaviour and degree of malignancy. In benign variants the survival prospects for patients are quite high, while in the case of malignant gliomas few patients are expected to live longer than a year.

In 2007 the group of Prof. Kami?ska showed that malignant gliomas can "re-program" the brain immune cells (microglia) to support tumour development instead of fighting it. Similarly the tumour even changed the protective immune cells recruited to the brain from blood and bone marrow (peripheral macrophages). The research to understand how the tumour deceives the host's immune system and forces the microglial cells to support and foster its growth has taken several years.

The results of other research groups showed that in the case of breast cancer the factor responsible for changing the behaviour of tumour-infiltrating macrophages is the CSF1 protein, controlling the maturation of macrophages. Researchers from the Nencki Institute asked, whether a similar substance is not produces by the cells of the malignant gliomas.

Studies conducted by Prof. Kami?ska's group has shown that gliomas do

not produce larger amounts of the CSF1 protein and this protein does not significantly impact tumour development. They were however lucky to discover the production of a different protein from the same family, the CSF2 protein. In benign tumours this protein was present in small amounts, while in malignant gliomas large amounts of it were discovered. Researchers from the Nencki Institute decided to investigate, whether this protein really influences tumour invasiveness. With the help of self-developed tools they turned off the gene responsible for the production of the CSF2 protein in glioma cells.

"We have observed that after turning off a single gene – the gene producing the CSF2 protein – the tumour cells stopped attracting the microglia and were not capable of converting these cells to support the tumour's development. As a result the immune system started working as expected and the malignant tumour was transformed into a benign form. It did not disappear, but stopped growing", says a PhD candidate Ma?gorzata Sielska from the Nencki Institute.

The protein responsible for "re-programming" the anti-tumour response and for high invasiveness of gliomas is present only in cancerous cells and is practically absent from healthy brain. Therefore researchers from the Nencki Institute suspect that when the gene responsible for its production is turned off in the brain, it would affect only the tumour.

Research on taming malignant brain tumours and converting them into benign forms has been conducted on mouse glioma cells growing in the brains of experimental animals, and published in the *Journal of Pathology*. Presently the group of Prof. Kami?ska is checking the effectiveness of this method in the cells of human malignant gliomas. Preliminary results confirm that silencing one gene in human glioma cells growing in mouse brains also stops the growth of the tumour. Developing tools to turn off this gene's expression, following the creation of appropriate carriers, will in the future open new possibilities

for gene therapy in humans.

The findings has helped Nencki researchers develop small molecules (short peptides) which interfere with binding the CSF2 protein (expressed by tumorous cells) to the appropriate receptors on microglial cells. This way the signal coming from tumorous cells gets blocked and the microglia is prevented from "re-programming" itself. The developed molecules, together with relevant genetic tools, are covered by an international patent. Presently researchers work towards starting preclinical and clinical trials of this method.

The proposed solution holds great potential for therapies using small molecules – short peptides or in the case of gene therapy, short RNA silencing gene expression. Will this method really work? This will be confirmed by further experiments and tests. For Nencki researchers it is important that the patented molecules target only one fragment of the signalling pathway which functions between the cells of the malignant tumour and the microglia, thus guaranteeing that no other functions of the organism are affected. Moreover discovery of such an important signalling pathway encourages scientists to search for ways of blocking it in other places, which could be technically more feasible.

"Our research is investigative in nature and above all aims to explain why and how tumours develop. We conducted our research mostly on experimental models, mouse glioma cells or human glioma cells growing in mice. Therefore the road to develop drugs and therapies limiting the invasiveness of gliomas in human is still very long. Luckily we already discovered the molecule that is worth targeting", sums up Prof. Kami?ska.

Provided by Nencki Institute of Experimental Biology