

Researchers discover the Achilles' heel of an aggressive brain cancer

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Glioblastoma cells (red) are known to invade the brain (blue). Figure shows patient-derived glioblastoma in murine brain treated with saline (control). Credit: Laakkonen Lab/University of Helsinki

Glioblastoma is the most prevalent and also the most lethal type of brain tumour in adults, with no curative treatment currently available. Glioblastomas cannot be surgically completely excised, as the tumour cells are adept at invading tissues and spreading around the brain. In



addition, glioblastoma cells are extremely resistant to existing drug therapies.

For a long time, researchers have been looking for weaknesses in <u>glioblastoma cells</u> which could be targeted with efficacious therapies.

A research group headed by Professor Pirjo Laakkonen at the University of Helsinki has already earlier found that the expression of a small fatty acid-binding protein (MDGI, or FABP3) in <u>glioblastoma</u> cells increases their ability to invade tissues and is linked with a poorer prognosis for the patient.

"Our new research revealed that glioblastoma cells depend on the expression of a gene which produces the MDGI protein. Inhibiting the function of this gene results in the death of the <u>tumour</u> cells," Laakkonen explains.

The absence of MDGI caused instability in the membranes of lysosomes, cleaning organelles found inside <u>tumour cells</u>, which, in turn, resulted in the leakage of acidic and <u>proteolytic enzymes</u> contained in the lysosomes into the cytoplasm, initiating cell death.

Further investigations of the mechanism leading to cell death revealed that silencing MDGI caused changes in the phospholipid composition of the lysosomes in glioblastoma cells. The transport of linoleic acid, a substance essential to humans found in food, from outside to inside cells was disturbed, resulting in a significant change to the fatty acid composition of the lysosomal membrane. This change apparently increased the permeability of the membrane.





Patient-derived glioblastoma in murine brain. Clemastine-treatment destroyed the invasive cells leading to clear tumor/brain border. Credit: Laakkonen Lab / University of Helsinki

"Our research demonstrates that MDGI is a key factor regulating and maintaining the structure of the lysosomal membrane. This is the first gene found to regulate the stability of the membrane," Laakkonen says.

What makes this finding particularly interesting is that cell death caused by leakage in the lysosomes of glioblastoma cells can be activated by using drugs that cross the blood-brain barrier. In their studies, Laakkonen's group used an antihistamine known as clemastine.

In cell cultures, clemastine resulted in lysosome-mediated <u>cell death</u> in glioblastoma cells already at concentrations which had no significant effect on healthy <u>cells</u> of different types. In mouse models, clemastine was very effective in reducing the spread of brain tumours and



improving the survival rate of the animals. In the case of the most invasive brain tumour model, the administration of clemastine resulted in the disappearance of the entire tumour.

"Our findings demonstrate that antihistamines and other drugs that increase the permeability of the lysosomal membrane can be considered as an enhancing therapy for patients with glioblastoma alongside established treatments," Laakkonen says.

More information: Vadim Le Joncour et al. Vulnerability of invasive glioblastoma cells to lysosomal membrane destabilization, *EMBO Molecular Medicine* (2019). DOI: 10.15252/emmm.201809034

Provided by University of Helsinki

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