The comments inserted into the following article are provided for discussion purposes with qualified bioinformatics professionals relative to mitophagy as the means of killing aggressive cancers in cells.

Note: The following link is provided relative to the use of checkpoint drugs that inhibit mitophagy as opposed to its activation.

https://www.cancernetwork.com/news/percentage-patients-benefit-immune-checkpoint-inhibitors-still-limited?rememberme=1&elq_mid=6775&elq_cid=337312&GUID=08CA590E-D499-4591-B8AA-DC553AF157AD

https://www.sciencedaily.com/releases/2019/05/190510094804.htm

Researchers discover the Achilles' heel of an aggressive brain cancer

Could antihistamine be a potential aid in defeating cancerous cells?

Date:

May 10, 2019

Source:

University of Helsinki

Summary:

Researchers have discovered a chink in the armor of the tumor cells of glioblastoma, a lethal brain cancer. Alongside the finding, the researchers also came up with a method for attacking this vulnerability. The results gained in experiments conducted with cell cultures and a mouse model are promising.

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 glioblastoma cells 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 glioblastoma cells increases their ability to invade tissues and is linked with a poorer prognosis for the patient.

MCFIP: FABP1 - Glutamic Acid, FABP2 - Proline and FABP3 - Glycine constitute the constituents of the DNA binding molecule DNAJB1. These findings should be correlated to the links between mutation of DNAJB1 and the ability of the mitochondria to be susceptible to cancer. Note: Cancer that impacts organelles relies upon lysosomes to encapsulate the organelle and mitophagy enzymes to “disassemble” it to allow for DNA self-replication to occur.

"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 tumour cells," Laakkonen explains.

The absence of MDGI caused instability in the membranes of lysosomes, **cleaning organelles found inside tumour cells**, which, in turn, resulted in the leakage of acidic and proteolytic enzymes 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.

"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 cell death in glioblastoma cells already at concentrations which had no significant effect on healthy cells 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.

The study was published in the distinguished *EMBO Molecular Medicine* journal.

Story Source:

Materials provided by **University of Helsinki**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Vadim Le Joncour, Pauliina Filppu, Maija Hyvönen, Minna Holopainen, S Pauliina Turunen, Harri Sihto, Isabel Burghardt, Heikki Joensuu, Olli Tynninen, Juha Jääskeläinen, Michael Weller, Kaisa Lehti, Reijo Käkelä, Pirjo Laakkonen. **Vulnerability of invasive glioblastoma cells to lysosomal membrane destabilization**. *EMBO Molecular Medicine*, 2019; e9034
DOI: 10.15252/emmm.201809034