Fighting tumors through sugar deprivation

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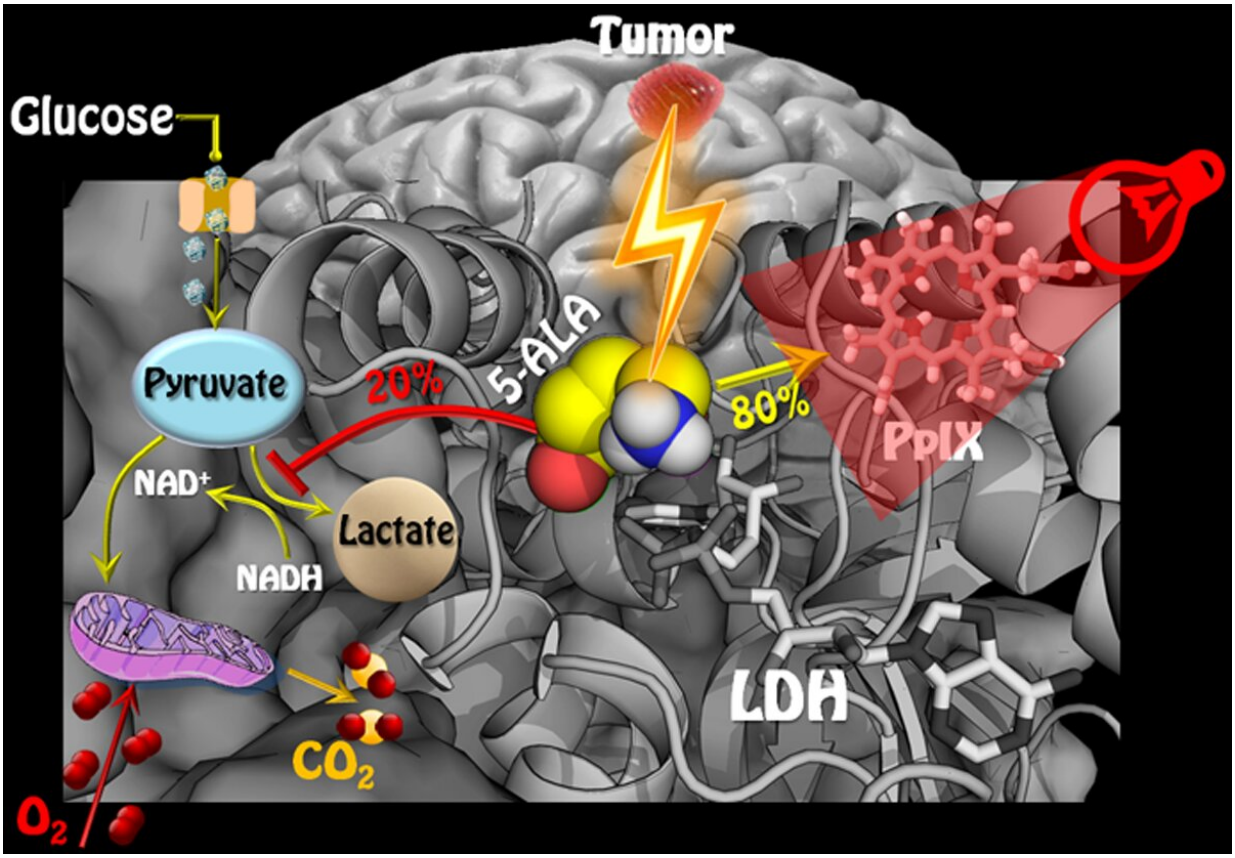

Credit: Oslo University Hospital

One of the deadliest forms of cancer is the brain tumor glioblastoma multiforme (GBM). It is a rare disease, with approximately 28,000 cases diagnosed every year in the EU and the US, for which median survival does not exceed one year, despite treatment. Less than 30% of adults

diagnosed with GBM survive one year after diagnosis, and only 3% of patients live longer than five years. Thus, GBM is also known as the Terminator. Current standard treatment for GBM consists of surgery followed by radio and chemotherapy.

GBM surgery is assisted by the use of fluorescent photosensitiser (PS) drugs which are conventionally used for photodynamic therapy. One such PS is Protoporphyrin IX (PpIX), a metadrug of exogenously administered 5-aminolevulinic acid (5-ALA) in the biochemical heme cycle. PpIX can precisely guide GBM resection as its prodrug 5-ALA very specifically accumulates in GBM lesions due to structural and functional differences in the vicinity of the GBM tumors. This is now standard practice in GBM resection, as approved by both the American Food and Drug Administration and the European Medicines Agency. Precise tumor resection can substantially increase patient survival.

Scientists in the Protonics Group at the Institute of Cancer Research at Oslo University Hospital, Norway, together with colleagues from NCSR Demokritos, Athens, Greece, have found that apart from being a photosensitive drug, 5-ALA is also a potent inhibitor of the glycolytic enzyme lactate dehydrogenase (LDH). This is a very important finding since most tumor cells draw energy from glycolysis, or the breakdown of glucose, in contrast to healthy cells which mainly obtain their energy from respiration. Interrupting the glycolysis in cancer cells can force them to die as they are unable to cover their energy needs from other sources. This is a well-established approach in cancer therapy, and LDH has been identified as a valuable target in many anticancer strategies.

The advantage of 5-ALA as an inhibitor of LDH, and consequently of glycolysis, is that it specifically accumulates in GBM tumors, tens of times more than in normal cells. Hence the disruption of the "sugar" breakdown in GBM cells that can lead to their demise. This development opens new avenues for GBM treatment and also potentially for other

types of cancer.

Dr. Theodossis Theodossiou, leader of the research team, said, "We are delighted to have uncovered this alternative property of 5-ALA. The fact that 5-ALA is approved for the detection of malignant gliomas and GBM makes our findings more valuable and easier to apply in the clinic. For detection purposes, 5-ALA is only applied to patients for a few hours, which is not enough to kill the cancer cells by glycolysis disruption. However, prolonged administration for one or several days could lead to surprising, even curative results, in a disease which is currently incurable and lethal."

The research is published in *Cancers*.

More information: Mantas Grigalavicius et al, 5-ALA Is a Potent Lactate Dehydrogenase Inhibitor but Not a Substrate: Implications for Cell Glycolysis and New Avenues in 5-ALA-Mediated Anticancer Action, *Cancers* (2022). DOI: 10.3390/cancers14164003

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