

Scientists use new approach to disable brain cancer cells' ability to survive

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The mTORC1 substrates 4EBP1/2 prevent cell death in response to glucose starvation in human, mouse and yeast cells. Credit: *Nature Communications* (2024). DOI: 10.1038/s41467-024-48386-y

When you disable the brakes on a race car, it quickly crashes. Dr. Barak Rotblat wants to do something similar to brain cancer cells. He wants to



disable their ability to survive glucose starvation. In fact, he wants to speed the tumor cells up, so they just as quickly die out. It is a novel approach to brain cancer based on a decade of research in his lab.

He, his students and co-lead researcher Gabriel Leprivier of the Institute of Neuropathology at University Hospital Düsseldorf published their findings in *Nature Communications* last week.

Until now, it was believed that cancer cells prioritized growth and rapid proliferation. However, it has been shown that there is less <u>glucose</u> in tumors vs. normal tissue.

If cancer cells are solely focused on reproducing at the fastest possible rate, then they should be more dependent on glucose than regular cells. However, what if their absolute top priority is survival rather than exponential growth? Then, triggering a burst of growth under glucose starvation could lead to the cell running out of energy to survive and dying out.

"It is an intriguing insight that comes after a decade of research," explains Dr. Rotblat. "We may be able to target just the cancer cells and not regular cells at all, which would be a very promising step forward on the path to personalized medicine and therapeutics that do not affect healthy cells the way chemotherapy and radiation do."

"Our discovery about glucose starvation and the role of antioxidants opens a therapeutic window to pursue a molecule which could treat glioma (brain cancer)," he adds. Such a therapeutic might also be able to treat other types of cancers.

Rotblat and his students, Dr. Tal Levy and Dr. Khawla Alasad began by considering that cells regulate their growth according to their available energy. When energy is plentiful, cells make fat and lots of proteins to



store energy and grow. When energy is scarce, they must pump the brakes and stop making fat and proteins or burn themselves out.

Tumors are mostly in a de facto state of glucose starvation. So, they began thinking about locating the molecular brakes that enable the cancer cell's survival in glucose starvation. If they could turn that off, then the tumor would die, but the regular cells, which are not glucosestarved, would remain unaffected.

So, Rotblat and his students followed the trail of a mTOR (Mamelian Target of Rapamycin) pathway. A pathway equipped with proteins that measure the energetic state of the cell and, accordingly, regulate <u>cell</u> growth. They found that a protein in the mTOR pathway, known to pump the brakes on protein synthesis when energy drops, 4EBP1, is essential for human, mouse, and even <u>yeast cells</u>, to survive glucose starvation.

They demonstrated that 4EBP1 does so by negatively regulating the levels of a critical enzyme in the fatty acid synthesis pathway, ACC1. This mechanism is exploited by cancer cells, particularly <u>brain cancer</u> cells, to survive in tumor tissue and generate aggressive tumors.

Dr. Rotblat is now working with BGN Technologies and the National Institute for Biotechnology in the Negev to develop a molecule that will block 4EBP1 forcing glucose-starved tumor cells to keep making fat and burn themselves out when they are glucose-starved.

More information: Tal Levy et al, mTORC1 regulates cell survival under glucose starvation through 4EBP1/2-mediated translational reprogramming of fatty acid metabolism, *Nature Communications* (2024). DOI: 10.1038/s41467-024-48386-y



Provided by Ben-Gurion University of the Negev

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