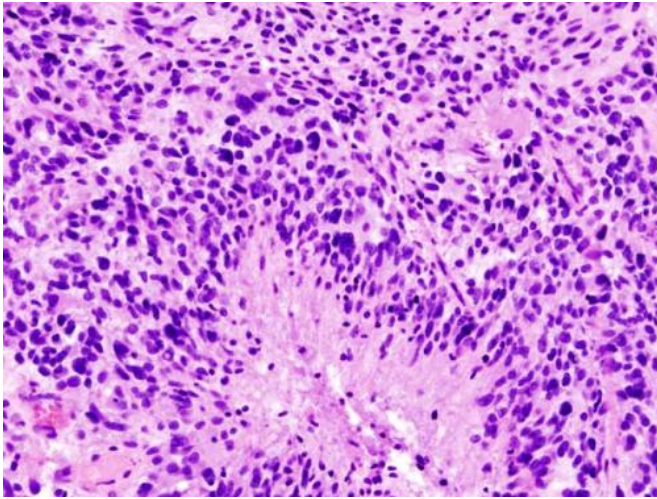


Glioblastoma study discovers protective role of metabolic enzyme, revealing a novel therapeutic target

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Glioblastoma (histology slide). Credit: Wikipedia/CC BY-SA 3.0

Researchers at The University of Texas MD Anderson Cancer Center have discovered a novel function for the metabolic enzyme medium-chain acyl-CoA dehydrogenase (MCAD) in glioblastoma (GBM). MCAD prevents toxic lipid buildup, in addition to its normal role in energy production, so targeting MCAD causes irreversible damage and cell death specifically in cancer cells.

The study was published today in *Cancer Discovery*, a journal of the American Association for Cancer Research. Preclinical findings reveal an important new understanding of metabolism in GBM and support the development of MCAD inhibitors as a novel treatment strategy. The researchers currently are working to develop targeted therapies against the enzyme.

"With altered metabolism being a key feature of glioblastoma, we wanted to better understand

these processes and identify therapeutic targets that could have real impact for patients," said lead author Francesca Puca, Ph.D., instructor of Genomic Medicine. "We discovered that glioblastoma cells rely on MCAD to detoxify and protect themselves from the accumulation of toxic byproducts of fatty acid metabolism. Inhibiting MCAD appears to be both potent and specific in killing glioblastoma cells."

To uncover metabolic genes that are key to GBM survival, the research team performed a functional genomic screen in a unique preclinical model system that permitted an *in vivo* study using patient-derived GBM cells. After analyzing 330 metabolism genes in this model, they discovered that several enzymes involved in fatty acid metabolism were important for GBM cells.

The team focused on MCAD because it was identified in multiple GBM models and found at high levels in GBM cells relative to normal brain tissue. In-depth studies determined that blocking MCAD in GBM cells resulted in severe mitochondrial failure caused by the toxic buildup of fatty acids, which normally are degraded by MCAD.

This resulted in a catastrophic and irreversible cascade of events from which GBM cells could not recover, explained senior author Andrea Viale, M.D., assistant professor of Genomic Medicine.

"It appears that the downregulation of this enzyme triggers a series of events that are irreversible, and the cells are poisoned from the inside," Viale said. "Usually, tumor cells are able to adapt to treatments over time, but, based on our observations, we think it would be very difficult for these cells to develop resistance to MCAD depletion."

While blocking MCAD appears to be detrimental to

the survival of GBM cells, the research team repeatedly found that normal cells in the brain were not affected by loss of the enzyme, suggesting that targeting MCAD could be selective in killing only cancer cells. Supporting this observation is the fact that children and animals born with an MCAD deficiency are able to live normally with an altered diet.

"It has become clear that MCAD is a key vulnerability unique to glioblastoma, providing us a novel therapeutic window that may eliminate [cancer cells](#) while sparing normal [cells](#)," said senior author Giulio Draetta, M.D., Ph.D., chief scientific officer and professor of Genomic Medicine. "We are looking for discoveries that will have significant benefits to our patients, and so we are encouraged by the potential of these findings. We are actively working to develop targeted therapies that we hope will one day provide an effective option for patients."

The research team has characterized the three-dimensional structure of the MCAD protein in a complex with novel small molecules designed to block the activity of the enzyme. As promising [drug candidates](#) are discovered, the researchers will work in collaboration with MD Anderson's Therapeutics Discovery division to study these drugs and advance them toward clinical trials.

More information: Francesca Puca et al. Medium-chain acyl CoA dehydrogenase protects mitochondria from lipid peroxidation in glioblastoma. *Cancer Discov.* May 26 2021 [DOI: 10.1158/2159-8290.CD-20-1437](#)

Provided by University of Texas M. D. Anderson Cancer Center

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