

# Metabolic compensation underlies drug resistance in glioblastoma

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Glioblastoma (GBM) is a highly aggressive brain tumor that is resistant to many conventional cancer therapies. The kinase mTOR induces pathways that are aberrantly activated in GBM. However, mTOR inhibitors have not shown much promise for treating GBM.

A new study in the *Journal of Clinical Investigation* indicates that mTOR inhibitor resistance in GBM is likely the result of compensatory glutamine metabolism.

Kazuhiro Tanaka and colleagues at Kobe University determined that glutaminase and glutamine levels increase in GBM cells and xenografts in response to mTOR inhibition. Combined inhibition of glutaminase and mTOR suppressed growth of GBM tumor xenografts.

Moreover, in patients with GBM, glutamine metabolism was increased in tumor tissue compared to noncancerous areas in the brain.

Together, these results suggest that combined targeting of mTOR and glutamine metabolism should be further explored as a therapeutic strategy for GBM.

**More information:** Compensatory glutamine metabolism promotes glioblastoma resistance to mTOR-targeted therapies, *J Clin Invest.* 2015;125(4):1591–1602. [DOI: 10.1172/JCI78239](https://doi.org/10.1172/JCI78239)

## Abstract

The mechanistic target of rapamycin (mTOR) is hyperactivated in many types of cancer, rendering it a compelling drug target; however, the impact of mTOR inhibition on metabolic reprogramming in cancer is incompletely understood. Here, by integrating metabolic and functional studies in glioblastoma multiforme (GBM) cell lines, preclinical models, and clinical samples, we demonstrate that the compensatory upregulation of glutamine metabolism promotes resistance to mTOR kinase inhibitors. Metabolomic studies in GBM cells revealed that glutaminase (GLS) and glutamate levels are elevated following mTOR kinase inhibitor treatment. Moreover, these mTOR inhibitor–dependent metabolic alterations were confirmed in a GBM xenograft model. Expression of GLS following mTOR inhibitor treatment promoted GBM survival in an  $\alpha$ -ketoglutarate–dependent ( $\alpha$ KG-dependent) manner. Combined genetic and/or pharmacological inhibition of mTOR kinase and GLS resulted in massive synergistic tumor cell death and growth inhibition in tumor-bearing mice. These results highlight a critical role for compensatory glutamine metabolism in promoting mTOR inhibitor resistance and suggest that rational combination therapy has the potential to suppress resistance.

Provided by Journal of Clinical Investigation

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