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Accelerated lipid catabolism and autophagy are cancer survival mechanisms under inhibited glutaminolysis

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**Abstract**

Suppressing glutaminolysis does not always induce cancer cell death in glutamine dependent tumors because cells may switch to alternative energy sources. To reveal compensatory metabolic pathways, we investigated the metabolome-wide cellular response to inhibited glutaminolysis in cancer cells. Glutaminolysis inhibition with C.968 suppressed cell proliferation but was insufficient to induce cancer cell death. We found that lipid catabolism was activated as a compensation for glutaminolysis inhibition. Accelerated lipid catabolism, together with oxidative stress induced by glutaminolysis inhibition, triggered autophagy. Simultaneously inhibiting glutaminolysis and either beta oxidation with trimetazidine or autophagy with chloroquine both induced cancer cell death. Here we identified metabolic escape mechanisms contributing to cancer cell survival under treatment and we suggest potentially translational strategy for combined cancer therapy, given that chloroquine is an FDA approved drug. Our findings are first to show efficiency of combined inhibition of glutaminolysis and beta oxidation as potential anti-cancer strategy as well as add to the evidence that combined inhibition of glutaminolysis and autophagy may be effective in glutamine-addicted cancers.

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