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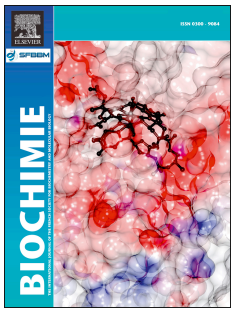

N-terminal phosphorylation of glutaminase C decreases its enzymatic activity and cancer cell migration

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Abstract

The mitochondrial phosphate-activated glutaminase C (GAC) is produced by the alternative splicing of the *GLS* gene. Compared to the other *GLS* isoform, the kidney-type glutaminase (KGA), GAC is more enzymatically efficient and of particular importance for cancer cell growth. Although its catalytic mechanism is well understood, little is known about how post-translational modifications can impact GAC function. Here, we identified by mass spectrometry a phosphorylated serine at the GLS N-terminal domain (at position 95) and investigated its role on regulating GAC activity. The ectopic expression of the phosphomimetic mutant (GAC.S95D) in breast cancer cells, compared to wild-type GAC (GAC.WT), led to decreased glutaminase activity, glutamine uptake, glutamate release and intracellular glutamate levels, without changing GAC sub-cellular localization. Interestingly, cells expressing the GAC.S95D mutant, compared to GAC.WT, presented decreased migration and vimentin level, an epithelial-to-mesenchymal transition marker. These results reveal that GAC is post-translationally regulated by phosphorylation, which affects cellular glutamine metabolism and glutaminase-related cell phenotype.