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

Carolline Fernanda Rodrigues Ascenção, Raghavendra Sashi Krishna Nagampalli, Zeyaul Islam, Matheus Pinto Pinheiro, Larissa Menezes dos Reis, Bianca Alves Pauletti, Carolina Aparecida de Guzzi Cassago, Daniela Campos Granato, Adriana Franco Paes Leme, Sandra Martha Gomes Dias



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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.

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