

## Impact of N-Terminal Protein Arginylation on Glioblastoma Progression and Therapy Resistance

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Post-translational modifications (PTMs) are critical regulators of cancer processes, including cell migration, adhesion, and proliferation. Protein N-terminal arginylation, an emerging PTM, has been implicated in tumor progression, although its mechanisms and effects vary by cancer type. Glioblastoma (GBM) is an aggressive intra-axial brain tumor associated with poor prognosis, poor survival, and a high recurrence rate. Here, we employed a multifaceted approach combining *in silico* analysis, *in vitro* experiments, and evaluation of patient samples to investigate the role of N-terminal arginylation in GBM progression. Our study involved manipulating ATE1 expression levels in the GBM-U87MG cell line through overexpression and silencing, followed by RNASeq, proteomics, immunofluorescence, and protein validation by immunoblotting. Data validation was performed in a second cell line (T98G) to corroborate these findings. Our results revealed a distinct arginylation pattern in GBM compared to non-neoplastic brain tissues. ATE1 upregulation was associated with increased tumor cell proliferation and a significant activation of the unfolded protein response (UPR) pathway. This activation favored autophagy over apoptosis, contributing to tumor cell survival and growth in both U87 and T98G models. Notably, inactivation of the UPR pathway in ATE1-silenced cells increased sensitivity to temozolomide (TMZ), a common therapeutic agent, in both drug-sensitive (U87) and drug-resistant (T98G) models. The expressions of key UPR and autophagy markers were validated in human GBM samples, further confirming the pivotal role of ATE1 in GBM pathophysiology. Our findings highlight protein arginylation as a novel crucial mechanism for GBM progression and suggest potential therapeutic strategies targeting the UPR pathway to improve treatment outcomes.

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