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DECIPHERING THE ROLE OF ULK1 IN THE BIOLOGY OF GLIOBLASTOMA MULTIFORME

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ULK1 is an evolutionarily conserved serine/threonine kinase, established as a key regulator of autophagy initiation. However, accumulating evidence indicates that ULK1 exerts broader scaffold and signaling functions beyond the autophagic machinery, modulating immune pathways, metabolic reprogramming, and cellular stress responses, thereby supporting a pleiotropic function that is, at least in part, independent of its canonical function in autophagy. Recent evidence indicates that ULK1 dysregulation may be involved in gliomas; however, its precise role in tumor progression, non-autophagic signaling pathways, and resistance to therapy remains poorly understood.

In this context, the present study aims to elucidate the role of ULK1 protein in the biology of glioblastoma multiforme (GBM). Thus, tumoral phenotype was correlated with ULK1 expression, and GBM tumorigenicity was evaluated in relation to ULK1 dosage.

Our results highlighted a significant modulation of ULK1 mRNA and protein in patient-derived tissue samples and in GICs-enriched GBM cells. Notably, in silico analysis of publicly available patient datasets revealed that lower ULK1 expression significantly correlated with reduced overall survival, suggesting its potential prognostic relevance. In in vitro experiments, we found that genetic and pharmacological modulation of ULK1 strongly impacts on GBM tumorigenic properties, independently on autophagy process. Further analysis will aim to elucidate molecular mechanisms and cellular processes underlying ULK1-driven effects, with a particular focus on defining its autophagy-independent signaling roles, highlighting its contribution to GBM progression.

Collectively, these findings identified ULK1 as a key regulator of GBM progression and provide a rationale for targeting ULK1-dependent pathways as a potential therapeutic strategy in the biological complexity of GBM.

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