RECKvar3 in Glioblastoma: Insights into Its Potential as a Prognostic Biomarker and Therapeutic Target

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Background: Glioblastoma is the most common and aggressive primary malignant brain tumor in adults, characterized by extensive intratumoral heterogeneity, diffuse infiltration, rapid progression, and poor prognosis despite the current standard of care, which includes surgical resection, radiotherapy, and temozolomide. Median overall survival remains approximately 15 months, underscoring the urgent need to identify the molecular mechanisms underlying tumor progression and therapeutic resistance. Alternative splicing is a major source of transcriptomic diversity and has emerged as a key regulator of tumor biology. Alterations in splicing patterns have been associated with multiple hallmarks of cancer, including cell proliferation, invasion, and treatment resistance, making splicing dysregulation a promising source of prognostic biomarkers and therapeutic targets.

Method: In vitro functional assays were performed using human glioblastoma cell lines genetically modified to overexpress RECKvar3, with anchorage-independent growth assessed by soft-agar colony formation. Transcriptomic and clinical data from TCGA glioma cohorts were analyzed to investigate RECK and RECKvar3 expression, their association with patient survival, and related biological processes through functional enrichment analyses.

Results: Our group previously identified multiple transcript variants of the *RECK* gene, including RECKvar3, a novel alternatively spliced transcript with potential biological significance. Using in vitro glioblastoma models, we demonstrated that RECKvar3 overexpression promotes enhanced anchorage-independent colony formation. Integrative analyses of The Cancer Genome Atlas (TCGA) dataset demonstrated that a high RECK/RECKvar3 expression ratio is associated with improved overall survival in patients with glioma. More recently, functional enrichment analyses based on RNA-sequencing data from 681 glioma patients associated RECK and RECKvar3 with extracellular matrix remodeling and signaling pathways, including Wnt signaling, supporting the hypothesis that alternative splicing functionally diversifies RECK-mediated signaling.

Conclusion: Collectively, these findings suggest *RECK* alternative splicing as a clinically relevant layer of gene regulation in glioma and support RECK splice variants as promising biomarkers and potential therapeutic targets for precision oncology.