Construction and Validation of a Novel Transdifferentiation Index Based on NOTCH1 and ADORA3 as a Prognostic Model for Glioblastoma

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Abstract

Background Glioblastoma (GBM) is an invasive primary brain tumor. Abnormal angiogenesis causes treatment resistance and unfavorable prognosis. Tumor stem cell-endothelial transdifferentiation is a vital angiogenic pathway; thus, discovering key molecular markers and building valid prognostic models is clinically valuable. *Methods* GBM clinical data were retrieved from CGGA, TCGA and Murat (GSE7696) datasets. Kaplan-Meier survival, univariate and multivariate Cox regression screened core genes from 12 transdifferentiation-related candidates. We constructed a GTN transdifferentiation index based on NOTCH1 and ADORA3, then established an integrated risk model and nomogram combined with clinical indicators. TCGA and Murat cohorts served as external validation sets. ROC curves and DCA evaluated predictive efficacy and clinical practicability. TIMER analyzed gene expression-immune infiltration correlations, while Western blot, tube formation and LDL uptake assays verified gene functions in vitro. *Results* NOTCH1 and ADORA3 were independent prognostic biomarkers for GBM. The GTN index and integrated risk model achieved robust predictive power across training and validation groups (AUC > 0.7), with higher risk scores corresponding to shorter overall survival. TIMER results indicated NOTCH1/ADORA3 expression correlated with CD4+ T cell and macrophage infiltration. Knockdown of either gene suppressed glioma cell tube formation and LDL uptake, impairing endothelial transdifferentiation capacity. *Conclusion* This study first validates NOTCH1 and ADORA3 as independent prognostic biomarkers for GBM and constructs a clinically applicable GTN index risk model for individualized survival evaluation. Their links to tumor immune microenvironment and transdifferentiation mechanism lay theoretical foundations for novel combined targeted therapies against GBM angiogenesis.

Keywords

Glioblastoma, Transdifferentiation of Tumor Cells, NOTCH1, ADORA3