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ΔNp73/ETS2 complex drives Angiopoietin-1 and Tie2 expression to promote angiogenesis in glioblastoma

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Glioblastoma multiforme (GBM), high-grade gliomas that arise from the brain's supportive tissue, represent the most common malignant brain tumor in children and adults with a median survival of 15 month after diagnosis. DNA copy number and gene expressions are known to differ in glioblastomas arising in children and adults3, yet we here report that both adult and pediatric GBMs aberrantly overexpress the oncogenic isoform ΔNp73. Malignant gliomas are dependent on angiogenesis and invasion and previous studies showed that increased expression of Angiopoietin-1 and its receptor Tie2 regulate GBM-induced angiogenesis. However, the mechanism driving elevated Angiopoietin-1 and Tie2 level in glioblastoma remained unclear. Our studies show, that ΔNp73 induces both Angiopoietin-1 and Tie2 expression in GBM, exerting thereby angiogenic functions. We determined that ΔNp73 upregulates both Angiopoietin-1 and Tie2 transcriptionally through ETS conserved binding sites on the promoters by interacting with ETS2. We demonstrated that expression of ΔNp73 correlated with GBM angiogenesis, cellular invasion and survival in orthotopic brain tumor models, whereas inhibition of ΔNp73 expression abrogated these oncogenic abilities. Together, this work provides important evidence about the underlying mechanism of elevated Angiopoietin-1 and Tie2 expression and presents an attractive opportunity for therapeutic intervention in both adult and pediatric glioblastomas.

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