ABSTRACT

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Integrated longitudinal analysis of adult grade 4 diffuse gliomas with long-term relapse interval revealed upregulation of TGF-β signaling in recurrent tumors.

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BACKGROUND: Adult-type diffuse gliomas, CNS WHO grade 4 are the most aggressive primary brain tumors and represent a particular challenge of therapeutic intervention.

METHODS: In a single-center retrospective study of matched pairs of initial and post-therapeutic glioma cases with a recurrence period greater than one year, we performed whole exome sequencing combined with mRNA and microRNA expression profiling to identify processes that are altered in recurrent gliomas.

RESULTS: Mutational analysis of recurrent gliomas revealed early branching evolution in seventy-five percent of patients. High plasticity was confirmed at the mRNA and miRNA levels. SBS1 signature was reduced and SBS11 was elevated, demonstrating the effect of alkylating agent therapy on the mutational landscape. There was no evidence for secondary genomic alterations driving therapy resistance. ALK7/ACVR1C and LTBP1 were upregulated, whereas LEFTY2 was downregulated, pointing towards enhanced Tumor Growth Factor β (TGF-β) signaling in recurrent gliomas. Consistently, altered microRNA expression profiles pointed towards enhanced Nuclear Factor Kappa B and Wnt signaling that, cooperatively with TGF-β, induces epithelial to mesenchymal transition (EMT), migration and stemness. TGF-β-induced expression of pro-apoptotic proteins and repression of anti-apoptotic proteins were uncoupled in the recurrent tumor.

CONCLUSIONS: Our results suggest an important role of TGF-β signaling in recurrent gliomas. This may have clinical implication, since TGF-β inhibitors have entered clinical phase studies and may potentially be used in combination therapy to interfere with chemoradiation resistance. Recurrent gliomas show high incidence of early branching evolution. High tumor plasticity is confirmed at the level of microRNA and mRNA expression profiles.

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