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**Stem-cell-like glioma cells are resistant to TRAIL/Apo2L and exhibit down-regulation of caspase-8 by promoter methylation.**

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Tumour necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL/Apo2L) is a promising cancer drug. However, many tumours are resistant to TRAIL-based therapies. Glioma cells with stem cell features (SCG), such as CD133 expression and neurosphere formation, have been recently identified to be more resistant to cytotoxic drugs than glioma cells lacking stem-cell-like features (NSCGs). Here we report that SCGs are completely resistant to 100-2,000 ng/ml TRAIL, whereas NSCGs revealed a moderate sensitivity to TRAIL. We found that SCGs exhibited only low levels of caspase-8 mRNA and protein, known to be indispensable for TRAIL-induced apoptosis. In addition, we detected hypermethylation of CASP8 promoter in SCGs, whereas NSCGs exhibited a non-methylated CASP8 promoter. Reexpression of caspase-8 by 5-Aza-2'-deoxycytidine was not sufficient to restore TRAIL sensitivity in SCGs cells, suggesting that additional factors cause TRAIL resistance in SCGs. Our data suggest that therapy with TRAIL, either as monotherapy or in combination with demethylating agents, is not effective in treating glioblastoma because SCGs are not targeted by such treatment.

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