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Gliosarcoma Stem Cells Undergo Glial and Mesenchymal Differentiation In Vivo.

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Cancer stem cells (CSCs) are characterized by their self-renewing potential, and by their ability to differentiate and phenocopy the original tumor in orthotopic xenografts. Long term propagation of glioblastoma (GBM) cells in serum containing medium results in loss of the CSCs and outgrowth of cells genetically and biologically divergent from the parental tumors. In contrast, the use of neurosphere assay, a serum-free culture for selection and propagation of CNS-derived stem cells, allows the selection of a subpopulation containing CSCs.

Gliosarcoma (GS), a morphological variant comprising approximately 2% of GBMs, present a biphasic growth pattern, composed of glial and metaplastic mesenchymal components. To assess whether the neurosphere assay would allow the amplification of a subpopulation of cells with "gliosarcoma stem cell" properties, capable of propagating both components of this malignancy, we have generated neurospheres and serum cultures from primary GS and GBM surgical specimens. Neurosphere cultures from GBM and GS samples expressed neural stem cell markers Sox2, Msi1 and Nestin. In contrast to the GBM neurosphere lines, the GS neurospheres were negative for the stem cell marker CD133. All neurosphere lines generated high grade invasive orthotopic tumor xenografts, with histological features strikingly similar to the parental tumors, demonstrating that these cultures indeed are enriched in CSCs. Remarkably, low passage GS serum cultures retained the expression of stem cell markers, the ability to form neurospheres, and tumorigenicity. The GS experimental tumors phenocopied the parental tumor, exhibiting biphasic glial and mesenchymal components, constituting a clinically relevant model to investigate mesenchymal differentiation in GBMs.

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