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Heterogeneity of stem-like human glioma cells
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Glioblastoma multiforme (GBM) is one of the most lethal solid tumors. GBMs grow invasively, develop resistance to radiation and chemotherapy, and frequently recur. Recently, glioma were classified into four distinct molecular entities, the classical, mesenchymal, neural and proneural subtype based on genomic and transcriptomic data obtained with brain tumor tissue. It remains unclear whether stem-like glioma cells, which constitute a small subfraction of the brain tumor cells, could be grouped into similar categories. We analyzed the features of stem-like glioma cells from glioblastoma, gliosarcoma, astrocytoma, oligodendroma and oligoastrocytomas. Primary cultures of glioblastoma and gliosarcoma consisted of varying amounts of different cell types. Growth in serum-depleted medium containing the growth factors EGF and bFGF resulted in progressive enrichment of stem-like cells. Co-expression of the intermediary filaments Nestin and GFAP as well as prominin-1/CD133, factors typically found in adult neural stem cells/progenitors, was observed only in a subfraction of stem-like cells and expression of the transcriptional regulator Sox-2 varied largely. In keeping with their stemness features, coexpression of Nestin and the stemness factors Nanog or Oct4 was detected in all populations of stem-like tumor cells. Expression of neurofilaments, doublecortin, DLX, Pax6, PSA-NCAM and other neural markers was additionally observed, suggesting that the majority of the populations of stem-like cells would belong to a neural or proneural group. mRNAs of the factors Myc, Gli, PTEN, Rest, Hif1α and p53, which affect stemness and tumorigenicity, respectively, were detected in all populations of stem-like cells. The major differences, however, concerned the protein expression levels. In particular, the level of p53 protein varied largely, even though p53 RNA was present in all primary cultures, suggesting malfunctioning of the p53-pathway in a subset of glioma cells. In addition, PTEN and AKT/PKB phosphorylation differed. Together our data reveals (i) a clear heterogeneity of stem-like glioma cells from different gliomas and gliosarcomas and (ii) differences between stem-like cells and their non stem-like counterparts from the same tumors.