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# Intratumoral Hypoxic Gradient Drives Stem Cells Distribution and MGMT Expression in Glioblastoma.

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### Abstract

Glioblastoma multiforme (GBM) are highly proliferative tumors currently treated by surgical removal, followed by radiotherapy and chemotherapy, which are counteracted by intra-tumoral hypoxia. Here we exploited image guided surgery to sample multiple intra-tumoral areas to define potential cellular heterogeneity in correlation to the oxygen tension gradient within the GBM mass. Our results indicate that more immature cells are localized in the inner core and in the intermediate layer of the tumor mass, while more committed cells, expressing GFAP and beta-III-tubulin, are distributed along the peripheral and neo-vascularised area, where Smad1/5/8 and Stat3 result to be activated. Moreover, GBM stem cells, identified with the stem cell marker CD133, express high level of DNA repair protein O6-methylguanine-DNA-methyltransferase (MGMT), known to be involved in chemotherapy resistance and highly expressed in the inner core of the tumor mass. Importantly, these cells and particularly CD133(+) cells result to be resistant to temozolomide (TMZ), the most used oral alkylating agent for the treatment of GBM, which specifically causes apoptosis only in GBM cells derived from the peripheral layer of the tumor mass. These results indicate a correlation between the intra-tumoral hypoxic gradient, the tumor cell phenotype and the tumor resistance to chemotherapy, leading to a novel concentric model of tumor stem cell niche, which may be useful to define the real localization of the chemo-resistant GBM tumor cells in order to design more effective treatment strategies.

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