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Sommario	Background: Glioblastoma multiforme (GBM) is the most common and lethal primary malignant brain tumor in adults. Angiogenesis is fundamental in GBM growth and progression. GBM can adopt different strategies to build up its vasculature. Moreover, the contribution of Glioblastoma Stem-like Cells (GSCs) to GBM-associated neovascularization have important implication in GBM angiogenesis. Targeting tumor vasculature has gained more and more attention as anti-cancer therapy and many strategies have been devised to inhibit angiogenesis in GBM as well. However, recent findings indicate that the effects of anti-angiogenic treatments are transient and that tumors become refractory and more aggressive. Hypothesis: GSCs directly contribute to tumor vasculature through trans-differentiation into functional endothelial-like cells. In addition, GSCs are able to partecipate to different processes within the vascular niche, emerging as potential escape mechanisms to counteract anti-angiogenic therapy. Among them, microvesicle-mediated intercellular communication represents a potent tool for tumor cells to influence the microenvironment promoting tumor growth and vascularization. In the vascular niche of irradiated brain, a symbiotic relationship might be hypothesized: GSCs allow the

	endothelial cells (ECs) to escape from radiation-induced senescence and the ECs provide differentiation cues to the tumor cells, driving its contribution to the angiogenic process. Both trans-differentation and microvesicles trafficking might contribute to the infiltrative shift observed after bevacizumab treatment, together with other mechanisms not yet completely characterized. The investigation of this process at a molecular level could provide useful information concerning novel potential targets for alternative anti-angiogenic therapies. Aims: The purpose of this project is the study of GSC contribution to tumor angiogenesis and resistance to anti-angiogenic therapy, through an integrated strategy: molecular characterization of GSC-derived endothelial cells (GdECs); investigation of the role of MVs within the vascular niche, and in particular in the crosstalk between GSCs and ECs; study of the mechanisms underlying development of bevacizumab resistance. Results: Molecular characterization of GSC-derived endothelial cells (GdECs) in vitro, in association with a drug screening performed on these tumor cells demonstrated that GdECs are characterized by strong survival signals that confer resistance to targeted inhibition. However, we identified the oxidative stress inducer Elesclomol as the most successful antiproliferative agent on GdEC survival, suggesting that targeting the oxidative stress pathway may represent an effective strategy. Study of the microvesicle-mediated crosstalk between GSCs and endothelial cells as emergent escape mechanism, revealed that radiation affects MV release, suggesting that it may induce modification of MV content as well. Investigation at molecular level of the bevacizumab-induced infiltrative shift revealed that tumor cells acquire a stem-like phenotype and vascular-like behaviors after treatment. In this process, PLXDC1/TEM-7 plays an important role as responsible of perivascular spreading induced by bevacizumab. Conclusions: The molecular characterization of the different mechanisms of GSC contribution to tumor vascularization provides useful insights into the development of alternative anti-angiogenic therapeutic strategy in GBM.
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