Irradiation-induced transdifferentiation of Glioblastoma Stem Cells into endothelial cells

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Purpose:
Glioblastomas (GBM) are brain tumors which display a bad prognosis despite conventional treatment associating surgical resection and subsequent radio-chemotherapy. Indeed, these invasive tumors recur almost inevitably. The presence of a radioresistant and tumorigenic GBM Stem-like Cells (GSC) subpopulation could contribute to explain this clinical impasse and the recurrence of these tumors. Furthermore, GBM are characterized by an important and abnormal vascularization and it has been shown that GSC could transdifferentiate into Tumor Derived Endothelial Cells (TDEC)1,2 which are key compounds of tumor growth. We hypothesized that ionizing radiation is able to facilitate transdifferentiation of GSC into TDEC. TDEC appearing within the irradiation field could thus participate to the formation of new vessels and could help remaining tumor cells to develop a new aggressive tumor.

Experimental Design:
We used GSC primocultures from several patients to cultivate irradiated or non-irradiated GSC under endothelial condition to obtain TDEC. Their endothelial features were then analyzed.

Results:
Although irradiation did not influence endothelial phenotype of TDEC, we showed that the endothelial functions of TDEC obtained from irradiated GSC (TDEC IR+) were improved (formation of pseudotubes in Matrigel™ and migration towards VEGF). Transcriptomic analysis of TDEC IR- and TDEC IR+ allowed us to highlight Tie2/Ang signaling pathway as an important actor of irradiation-induced transdifferentiation of GSC into TDEC. We are currently trying to confirm these results using different shRNA which inhibit Tie2 expression.

Conclusion:
Altogether these results suggest a new mechanism potentially involved in radioresistance of GBM. In the future, signaling pathways involved in this mechanism could be inhibited in order to decrease or even abolish GBM recurrence.

References :