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Hadrontherapy for glioblastoma: impact on tumor cells and on the healthy tissue

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Glioblastoma (GBM) are brain tumors resistant to conventional therapies, in particular to radiotherapy based on X-rays. Therefore, the use of hadrontherapy appears as very appealing strategy thanks to their finite dose deposition to spare normal brain tissue but also to their greater biological efficacy toward radioresistant tumor cells and their low sensitivity to hypoxia, a well know factor of radioresistance.
Here, we evaluated in vitro the effects of high-LET particles, especially carbon ions on hypoxia induced radioresistance. Hypoxia-induced radioresistance was studied in two human GBM cells (U251, GL15) exposed to X-rays or to carbon ion beams with various LET (28, 50, 100 keV/µm). Cell survival, radiobiological parameters and cell cycle, were assessed under those conditions. These results demonstrate that, although CIRT is more efficient than X-rays in GBM cells, hypoxia can limit CIRT efficacy in a cell-type manner that may involve cell-specific pathways. These results also confirm that other mechanisms in parallel to hypoxia are involved in radioresistance.
Glioma stem cells (GSC) are suspected to be the most radioresistant cells due to their quiescent state and high efficacy in DNA repair pathways. The number of GSC increases after radiotherapy and is associated with the risk of recurrence. This increase in GSC could result from dedifferentiation of tumor cells after X-ray irradiation. The impact of hadrontherapy on tumor cell dedifferentiation is less documented. We therefore studied the effect of different radiation modalities on this dedifferentiation capacity in human GBM cells (U87-MG). Interestingly, our results show that protons and in a less manner carbon ions decrease the formation of sphere contrary to X-rays. We are now conducting experiments to test whether the combination of radiation and hypoxia targeting agents could improve the effects of radiation alone.
Lastly, while hadrons appear of main interest to spare normal tissue due to ballistic properties, the effects on non-tumor tissues remain to be determined. It is important to question the potential effects of these new treatment modalities on cerebral cells. Preliminary results on various cells derived from normal brain will also be presented.

In conclusion, our study shows while targeting HIF pathways could rather be interesting in presence of X-rays. The use of hadrons limits the dedifferentiation ability of GBM. Thus, hadrontherapy seems to be a promising therapy to limit resistance and thus target the recurrence of GBM.

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