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Hadrontherapy to target glioblastoma stem cells to overcome radioresistance

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Glioblastoma (GBM) are brain tumors resistant to conventional therapies, in particular to radiotherapy based on X-ray. 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. Moreover, hypoxia also favors the dedifferentiation of GBM cells into GSC. Hadrontherapy is well known to be less dependent on the oxygen effect, but its impact on tumor cell dedifferentiation is less documented.
Therefore, we have evaluated in vitro, the effect of hadrons (protons and carbon ions), in combination or not with hypoxia-inducible factor (HIF) inhibitors, on the dedifferentiation capacity of GBM tumor cells (U87-MG) into GSC.
First, we confirmed that GBM cells are able to form spheres that express stemness and hypoxic markers. Secondly, we studied the effect of different radiation modalities on this dedifferentiation capacity. Interestingly, our results showed that hadrons decreased the formation of spheres contrary to X-rays. Then, as the spheres express hypoxic markers, we evaluated the impact of targeting intracellular hypoxia on this dedifferentiation capacity. Without radiation, we did not show any effect of HIF inhibitors on the formation of spheres. Lastly, we tested whether the combination of radiation and hypoxia targeting could improve the effects of radiation alone. Surprisingly, the inhibition of HIF decreased sphere formation after X-rays, but did not improve the efficacy of hadrons to further reduce sphere formation.
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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