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Impact of Hypoxia and Hadrontherapy on Radioresistant Chondrosarcoma Cancer Stem Cells

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Abstract

Chondrosarcoma is a malignant tumor characterized by an abundant extracellular matrix, which is responsible of a hypoxic microenvironment. Hypoxia can lead to resistance of conventional X-rays treatment by the absence of oxygen, essential for the formation of Reactive Oxygen Species (ROS) associated with cellular toxicity. Hypoxia is also related to a possible stabilization of subpopulation of Cancer Stem Cells (CSCs) possibly implicated in radioresistance [1]. Hadrontherapy is expected to induce more damage under a hypoxia environment, according to the characteristics of ions, but the effect of hadrons on the CSCs needs to be further analyzed.

For this study, the impact of the different irradiations qualities (X-rays, protons and carbon ions) under low (1%) and high (20%) oxygen conditions were analyzed on 2 chondrosarcoma cell lines: L835 and Oums27 [2], respectively muted on IDH1 and p53. Cell survival was evaluated by clonogenic assay and the impact of treatments on CSC subpopulation was studied using an ALDH activity test by flow cytometry and a tumorsphere assay.

As expected, hypoxia decreased X-rays efficacy on both chondrosarcoma cell lines. This effect was less evident with proton and carbon ions irradiations, excepted in case of the L835 cells irradiated with carbon ions. Without irradiation, hypoxia increased ALDH-high cells only with Oums27 cells. After a high dose (3Gy) of carbon ions, an increased of the ALDH-high population was observed with Oums27 cells, in both oxygen conditions. Using L835 cells, an increase of the ALDH-high population was also observed with hypoxic culture condition, independently of the dose (1 to 3Gy).

This preliminary study shows a differential impact of hypoxia on chondrosarcoma cells survival after X-rays, protons and carbon ions irradiations. The corresponding radioresistance

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could be linked with a CSC subpopulation.

1. Vares G, Ahire V, Sunada S, Ho Kim E, Sai S, Chevalier F, et al. *Radiother Oncol.* 2020;150:253–61.
2. Chevalier F, Hamdi DH, Lepleux C, Temelie M, Nicol A, Austray JB, et al. *Technol Cancer Res Treat.* 2019;18:153303381987130.