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Overcoming the resistance of head and neck squamous cell carcinoma to photon and carbon ion irradiation by targeting cancer stem cells

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Although hadrontherapy is a very promising alternative to conventional radiotherapy in a large variety of cancers, recent clinical trials have shown that local control of head-and-neck squamous cell carcinoma (HNSCC) is worse than expected due to loco-regional recurrence of the tumor. In order to obtain more insight into the mechanisms of tumour escape, we have investigated the role of cancer stem-like cells (CSlC) obtained from the SQ20B radioresistant HNSCC cell line (SQ20B). According to the literature, we have shown that the resistance of CSlC may result from an imbalance between exacerbated self-renewal and proliferative capacities and the decrease in apoptotic cell death triggering. Attempts to modulate these processes seem therefore to be promising therapeutic strategies.

Concerning the self-renewal pathway, a fundamental role of Bmi-1 was demonstrated in SQ20B-CSlC for which its inhibition significantly enhanced sensitivity to high and low LET radiation by triggering apoptotic cell death. We have also demonstrated that the radioresistance of CSlC cells could result from their high proliferative capacity related to high aldehyde deshydrogenase (ALDH) activity. Inhibition of ALDH using all-trans retinoic acid induced differentiation of CSlC associated with a significant decrease in cell survival after either carbon or photon irradiation.

Regarding apoptosis, since irradiated CSlC do not undergo early apoptosis because of a transient arrest in G2/M followed by mitotic catastrophe, treatment of CSlC with the inhibitor of the G2/M arrest UCN-01 triggered early apoptosis thus leading to radiosensitisation after photon and carbon ion exposure.

The combination of ATRA and UCN-01 treatment with irradiation drastically decreased the survival fraction at 2 Gy (SF2) of SQ20B-CSlC from 0.85 after photon irradiation to 0.38. Furthermore, SF2 decreased from 0.45 in response to carbon ions to 0.21 when associated with ATRA and UCN-01.

In conclusion, whatever the pharmacological strategies used, an important radiosensitisation of CSlC was obtained. Adjuvant treatments targeting either the inhibition of survival/self-renewal pathways or the triggering of apoptosis should improve the results for patients treated with radio- or hadron- therapy.

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