**Role of HIF-1α in the resistance of Cancer Stem Cells to photon and carbon ion irradiations**

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Head-and-Neck-Squamous Cell Carcinoma (HNSCC) are resistant to standard treatments, partly due to Cancer Stem Cells (CSCs) localized in hypoxic niches. The protein HIF-1α (Hypoxia-Inducible Factor 1α) is considered as the major transcriptional regulator of the cellular response to oxygen homeostasis. Compared to X-rays, carbon ions relie on better ballistic properties, higher relative biological effectiveness and the absence of oxygen effect. HIF-1α is involved in the resistance to photons whereas its role in response to carbon ions remains unclear. My work aims at clarifying the role of HIF-1α in the response of CSCs to photon (250kV) and carbon ion (75Mev/n and 290Mev/µ) irradiations in normoxic or hypoxic (1% O2) conditions. For two HNSCC cell lines and their CSC subpopulation, in response to photons under hypoxia, an OER upper than 1.2 was associated with HIF-1α expression. This stabilization appears earlier in CSCs than in non-CSCs and is correlated with the variation of ROS levels, confirming the adaptive properties of CSCs to hypoxia. The diffuse ROS production by photons is concomitant with HIF-1α expression and essential to its activation. Compared with photons, the oxygen effect is canceled after carbon ion exposure (OER=1) and no stabilization of HIF-1α was observed in normoxia, probably due to the ROS localization in the track, insufficient to stabilize HIF-1α. Inhibition of HIF-1α with a siRNA leads to the decrease of HNSCC-CSC survival after both radiations in hypoxic conditions (OER<1). Furthermore, radiosensitization is associated with a significant increase of residual DSBs in response to both types of irradiations. Finally, CSCs migrate more and are more invasive than non-CSCs in normoxia and even more under hypoxia. Photon irradiation increases both process under normoxia whereas carbon ions decrease them significantly in normoxic and hypoxic conditions. The inhibition of HIF-1α, in response to both types of irradiations and particularly in hypoxic conditions, is associated with a low proportion of migrating and invasive cells, confirming the role of HIF-1α in the epithelio-mesenchymal transition. These results demonstrate that HIF-1α plays a key role in the response of CSCs and non-CSCs to photon and carbon ion irradiations. It participates to radioresistance by increasing cell survival, DNA repair and invasiveness and contributes to tumor escape. This makes the HIF-1α targeting an attractive therapeutic challenge.

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