

Different cell death pathways for radiosensitive and radioresistant HNSCC exposed to high or low LET radiation

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It is now well established that heavy ion radiotherapy can offer some potential merits over the conventional radiotherapy. The advantage of this new treatment modality lies on the physical and biological properties of carbon ions. It provides good dose localization (Bragg peak) in critical cancer tissue and gives higher relative biological effectiveness in cell killing. Taking advantage of these clinically relevant properties, a high number of patient have been treated with carbon ions, and the treatment results were found to be very promising. With this growing interest in hadrontherapy, it is highly important to investigate the mechanisms of action of carbon ions, in order to improve the outcome of this therapy. Thus, we initiated studies on the mechanisms of cell death in two p53-mutated head and neck squamous cell carcinoma (HNSCC) with opposite radiosensitivity following carbon ions and X-rays exposure, since recent clinical trials had shown that the local treatment of HNSCC by carbon hadrontherapy was much less efficient than that of other radioresistant cancers. We first demonstrated that carbon irradiation (9.8MeV/u) induced a higher level of clonogenic cell death than carbon (75MeV/u) and X-rays irradiation, for SCC61 (sensitive to X-rays), and SQ20B cells (resistant to X-rays) which are systematically less sensitive. We then showed that two distinct cell death pathways were induced in SCC61 and SQ20B cells after exposure to low and high LET. In SCC61 cells, a dose- and time-dependent induction of apoptosis was observed starting at 24 hours in response to X-rays which was even more pronounced in response to both carbon beams. This increase was p53 independent and directly related to that of ceramide production. In contrast, in SQ20B cells, a G2 phase arrest was the main cellular response on irradiation by carbon beams. It was more pronounced compared to X-rays irradiation SQ20B cells and associated with Chk1 activation and inhibition of cyclin B/cdc2 complex. Furthermore, 5 days after carbon ions irradiation, SQ20B cells bypassed the G2/M arrest and underwent mitotic catastrophe cell death. Although most of SQ20B cells underwent mitotic catastrophe, a subpopulation seemed to resist and to reenter the cell cycle. These results may explain the moderate tumor control observed in HNSCC patients treated by hadrontherapy compared to that obtained for other tumor entities. In addition preliminary results showed that inhibition of G2 arrest may sensitize the SQ20B cells to high LET irradiation further experiments are in progress.