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In vitro radiobiological effects of Radium-223

α-particle emitting radionuclides have been increasingly used in cancer treatment with particular interest for the treatment of micrometastases, due to the recently demonstrated survival benefit of Radium-223 (223Ra) in the treatment of bone metastases [1]. However, the reasons for its efficacy in comparison to previous beta emitters remains poorly understood. There is a pressing need to model and quantify α-emitter effects in pre-clinical models so the next generation of trials utilizing 223Ra can be optimally designed.

It is often assumed that the higher lethality of α-particles is related with the higher propensity for complex DNA double-strand breaks (DBSs) and clustered DNA damage in the irradiated cells. The present investigation was carried out to evaluate the radiobiological effect of 223Ra in 3 different prostate cell models (PC-3, U-2OS metastatic lines, and normal RWPE) by assays of clonogenic survival and DNA damage.
Clonogenic cell survival curves were analyzed for different cell lines after irradiation with 225 kVp X-rays from 0 to 8 Gy (dose rate 0.594 Gy/min), external α-particles (241 Americium) from 0 to 2 Gy (dose rate 1.579 Gy/min) and 223Ra from 0 to 0.5 Gy (dose rate 1.389 mGy/min).

The results showed a superior efficacy of 223Ra in comparison with the external α source in all cell lines but with a cell type dependency. The Relative Biological Effectiveness (RBE) for 50% survival for RWPE is 6.07 and 7.97, for external α- particles and 223Ra respectively. For U-2OS is 6.36 and 8.9 and finally for PC-3 the values are 3.63 and 7.47.

Lastly, the induction and repair of DNA damage by different radiation qualities was analyzed by immunofluorescence (53BP1) for doses up to 2 Gy and recovery times of 1, 4, 24 and 96h. For all irradiation setups there is a linear relationship between the number of foci and the absorbed dose. The level of induction and the shape of the kinetics curves are radiation- and cell-specific with the highest induction of foci observed after X-ray irradiation, the lowest after external α irradiation, and 223Ra being slightly higher than external α particles. In terms of repair, foci induced by external α source or 223Ra are repaired approximately 3.5 times slower than the X-ray induced breaks in the same cell line. These observations support the higher propensity for complex DNA-damage induced by heavy particles as reported in the literature.
Interestingly, exposure to 223Ra severely affects the nuclear structure with a significant number of giant nuclei, and a large fraction of cells undergoing mitotic catastrophe, features not seem to the same extent with external beam irradiation.

In conclusion, our results suggest that response to Radium-223 is cell-specific and that better effectiveness does not solely depend on the DNA damage complexity.

[1] Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med. 2013;369:213-223.

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