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Radiation-induced DNA Damage and Repair in Normal Thyroid Epithelial Cells: Comparison of Cell Cycle Stage

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The thyroid is considered to be among the most radiosensitive organs. However, the biological nature of thyroid radiosensitivity as compared to other organs is largely unknown. The interest of using high-LET radiation in cancer treatment has increased during recent years because of its high efficiency in inducing biological damage and beneficial dose distribution when compared to low-LET radiation. The high-LET alpha particle Astatine-211 (211At), that is concentrated in the thyroid by the same mechanism as 131I (NIS-mediated), has been proposed to be used as an alternative to 131I for therapeutic use. Of interest, 211At induces two to three times more DNA DSBs than low-LET irradiation in fibroblast cultures, making 211At an attractive source of internal radiation for comparative studies. As a result, we here study the radiation response, i.e. DSB repair, cell cycle checkpoint arrest and chromosomal aberrations in normal cycling versus stationary cells exposed to different radiation qualities. Both cycling and stationary primary pig thyrocytes cultured on petri dishes or chamber slides were exposed to low-LET (60Co) or high-LET (211At) radiation to absorbed doses of 0-3 Gy. Repair of DNA damages and cell cycle arrest were studied by detection of phosphorylated H2AX (gamma-H2AX) and phosphorylated Chk2 (pChk2 Thr68) with flow cytometry and western blotting. Micronuclei assay was used to detect chromosomal aberrations. The levels of gamma-H2AX and pChk2 (Thr68) decreases during the first 24 h in cycling cultures exposed to 60Co, whereas there are increasing levels in cycling cultures exposed to 211At. The decreasing levels in response to low-LET radiation might indicate DNA repair while the increasing levels in response to high-LET radiation possibly signify poor repair of DNA damage or formation of de novo DSBs during replication and DNA repair processing. The micronuclei assay shows that cycling cells irradiated with 211At (0-2 Gy) have an increasing ratio of micronuclei per cell nuclei up to 1 Gy. Doses above that tend to result in lower levels of micronuclei per cell, probably due to an efficient cell cycle arrest. Interestingly, cycling cells exposed to 1 Gy 211At get 9 times higher levels of micronuclei than cycling cells exposed to 1 Gy 60Co, giving a RBE of 9. The result indicates that thyrocytes might be a lot more sensitive to high-LET radiation than fibroblasts where a RBE of 3 has been found.

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