Radiobiological Effects of Alpha-Particles from Astatine-211

From DNA Damage to Cell Death

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av

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Avhandlingen baseras på följande arbeten:

I **Claesson K,** Stenerlöw B, Jacobsson L and Elmroth K. Relative Biological Effectiveness of the α-Particle Emitter ^{211}At for Double-Strand Break Induction in Human Fibroblasts. *Radiation Research* 2007; 167, 312-318.

II **Claesson K,** Magnander K, Kahu K, Lindegren S, Hultborn R and Elmroth K. RBE of α-Particles from ^{211}At for Complex DNA Damage and Cell Survival in Relation to Cell Cycle Position. *International Journal of Radiation Biology* 2011; 87, 372-384.

III **Claesson K**, Nordén Lyckesvärd M, Magnander K, Lindegren S and Elmroth K. Double-Strand Break Repair and Cell Cycle Arrest Activation in Stationary and Cycling Diploid Cells Irradiated with High- and Low-LET Radiation. *Manuscript*.

IV **Claesson K,** Nordén Lyckesvärd M, Magnander K, Delle U and Elmroth K. Effects on Micronuclei Formation and Growth Kinetics in Normal Fibroblasts after Irradiation with Alpha Particles and X rays: Differential Response in Stationary and Cycling Cell Cultures. *Manuscript.*

GÖTEBORGS UNIVERSITET

Radiobiological Effects of Alpha-Particles from Astatine-211

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ABSTRACT

In recent years, the use of high linear energy transfer (LET) radiation for radiotherapeutic applications has gained increased interest. Astatine-211 (^{211}At) is an α-particle emitting radionuclide, promising for targeted radioimmunotherapy of isolated tumor cells and microscopic clusters. To improve development of safe radiotherapy using ^{211}At it is important to increase our knowledge of the radiobiological effects in cells. During radiotherapy, both tumors and adjacent normal tissue will be irradiated and therefore, it is of importance to understand differences in the radioresponse between proliferating and resting cells. The aim of this thesis was to investigate effects in fibroblasts with different proliferation status after irradiation with α-particles from ^{211}At or X-rays, from inflicted DNA damage, to cellular responses and biological consequences.

Throughout this work, irradiation was performed with α-particles from ^{211}A or X-rays. The induction and repair of double-strand breaks (DSBs) in human normal fibroblasts were investigated using pulsed-field gel electrophoresis and fragment analysis. The relative biological effectiveness (RBE) of ^{211}At for DSB induction varied between 1.4 and 3.1. A small increase of DSBs was observed in cycling cells compared to stationary cells. The repair kinetics was slower after ^{211}At and more residual damage was found after 24 h. Comparison between cells with different proliferation status showed that the repair was inefficient in cycling cells with more residual damage, regardless of radiation quality. Activation of cell cycle arrests was investigated using immunofluorescent labeling of the checkpoint kinase Chk2 and by measuring cell cycle distributions with flow cytometry analysis. After α-particle irradiation, the average number of Chk2-foci was larger and the cells had a more affected cell cycle progression for several weeks compared with X-irradiated cells, indicating a more powerful arrest after ^{211}At. Flow cytometry showed that cycling cells were arrested in G_2/M while stationary cells underwent a delayed entry into S phase after release of contact inhibition. Radiation-induced chromosomal damage was studied by investigating the formation of micronuclei after first mitosis post-irradiation. Alpha-particles induced 2.7 and 4.1 times more micronuclei in cycling and stationary cells, respectively, compared with X-rays.

Induction of DSBs and cell survival after irradiation were also investigated in synchronized Chinese hamster fibroblasts. The cells were synchronized with mimosine in G_1, early, mid and late S phase and in mitosis. Cell survival was determined using the clonogenic assay. The radioresponse between cell cycle phases varied after both ^{211}At and X-rays, resulting in variations of RBE for ^{211}At between 1.8 and 3.9 for DSB induction and between 3.1 and 7.9 for 37% survival. The lowest RBE was observed in mitotic cells for both DSB induction and clonogenic survival.

In summary, for all endpoints studied α-particles from ^{211}At were more detrimental compared with X-rays. Further, the radioresponse was dependent upon the proliferation status of the cells at the time of irradiation, after both low- and high-LET radiation, resulting in variations of the relative biological effects.

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