



UNIVERSITY OF GOTHENBURG

Formation and repair of complex DNA damage induced by ionizing radiation

AKADEMISK AVHANDLING

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av

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Avhandlingen baseras på följande arbeten:

- I. **K. Magnander**, R. Hultborn, K. Claesson and K. Elmroth, Clustered DNA damage in irradiated human diploid fibroblasts: influence of chromatin organization. *Radiat. Res.* **173**, 272-282 (2010).
 - II. K. Claesson*, **K. Magnander***, H. Kahu, S. Lindegren, R. Hultborn and K. Elmroth, RBE of α -particles from ^{211}At for complex DNA damage and cell survival in relation to cell cycle position. *Int. J. Radiat. Biol.* **87**, 372-384 (2011)
- *Authors contributed equally to the work
- III. **K. Magnander**, U. Delle, M. Nordén Lyckesvärd, J. Kallin, J. Swanpalmer, A. Morgenstern, F. Bruchertseifer, H. Jensen, S. Lindegren and K. Elmroth. Repair of DSB and clustered damage: A study on influence of direct hits, chromatin acetylation and radiation quality. *Manuscript*.
 - IV. **K. Magnander** and K. Elmroth, Biological consequences of formation and repair of complex DNA damage. *Cancer Letters.* **327**, 90-96 (2012)

Formation and repair of complex DNA damage induced by ionizing radiation

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ABSTRACT

DNA is the critical target when cells are exposed to ionizing radiation, a potent stressor with capacity to produce complex DNA damages, thereby increasing the risk of cancer. DNA and associated histones form chromatin, which is an effective protection against ionizing radiation. We have investigated the formation and repair of complex lesions, including double strand breaks (DSB) and clustered damages (two or more lesions within 10-20 base pairs) after exposure to ionizing radiation of different beam qualities, in normal human cells. The biological consequences of clustered lesions are not fully understood.

We present a major influence of chromatin on induction of DSB and oxidized purine- and pyrimidine clusters. For example, sparsely ionizing radiation induces 170 times more clusters in naked DNA, compared with intact cells. For DSB, the same factor was 120. This reflects a pronounced influence of the indirect effect of radiation on clusters, supporting our finding that abolishment of radical scavengers, and suppression of the indirect effect, influence clusters more than DSB. Also, we investigated the repair of complex lesions (i) formed from direct DNA hits, (ii) in cells with hypo- or hyperacetylated chromatin or (iii) in cycling or non-proliferating cultures, conditions assumed to compromise removal of these lesions. We present a fast and efficient repair of clustered damage with no evidence of *de novo* DSB formation due to attempted repair. We observe no large influence of proliferation status. Surprisingly, no major influence of chromatin acetylation was found. Direct DNA hits did not influence repair of clusters but compromised DSB processing. We present that induction of DSB and cell survival is cell cycle dependent for densely ionizing radiation, in contrast to what was previously reported. Compared with sparsely ionizing radiation, α -particles induce more DSB and result in a decrease in cell survival. Also, the repair of DSB was compromised. Surprisingly, clusters induced by α -particles were rapidly repaired.

In conclusion, both DSB and clustered damage, formed by ionizing radiation, are sensitive to the antioxidant level in cells. There are two possible explanations for the observed efficient removal of clusters in normal cells, either the rapid decrease could be due to efficient repair or represent clusters too complex to be assessed in our method.

Keywords: Ionizing radiation, clustered damage, chromatin structure, DSB

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