Do the Auger Electron Emitters I-123 and I-125 Show Differences in their Cyto- and Genotoxic Potential?

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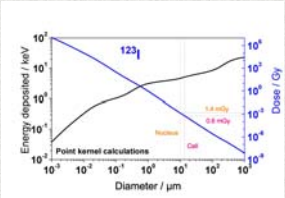
Objectives

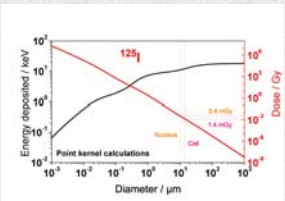
The Auger electron emitters (AEE) I-123 and I-125 are characterized by different half-lifes (13.2 h vs. 59.4 d) and mean numbers of Auger electrons emitted per decay (8 vs. 15) and allows to investigate the biological effectiveness of AEE in respect to energy deposited per decay and the dose rate. Micronucleus formation, chromatin damage and induction of cell cycle arrest were studied in synchronized human SCL-II and Jurkat cells labeled with various activity concentrations of I-123 UdR and I-125 UdR and compared to external γ-irradiation (Cs-137, 0.7 Gy/min).

Results and Conclusions

- **I-125 UdR caused a slightly stronger response in SCL-II cells than I-123 UdR regarding micronucleus formation (Cytochalasin B Micronucleus Assay) and chromatin damage (Alkaline Comet Assay) in respect to accumulated decays but not in respect to energy dose to the cell nucleus.**
- **I-123 UdR and I-125 UdR cause enhanced genotoxic effects when compared to external γ-irradiation (Cs-137, 0.7 Gy/min).**
- **I-125 UdR induced a permanent G2/M arrest in SCL-II cells at a decay rate as low as 1 decay every 120 seconds in the DNA/genome of a cell.**
- **In the low dose range AEE possess a 2- to 3-times stronger genotoxic potential when compared to high-dose rate γ-irradiation.**
- **The chosen microdosimetry approach is suitable for both AEE and explains their effectiveness in terms of energy deposited.**
- **The different dose rate of both AEE seems not to be reflected in the analyzed biological effects.**

Dosimetry





- The conversion of the energy deposition (black) into dose values (blue and red) results in an enormous dose range over several orders of magnitude so that the appropriate choice of the critical target is decisive for the dose determination. Here, the cell and the cell nucleus, respectively, were chosen resulting in the indicated ranges of energy doses.
- Based on 10000 Monte Carlo-simulated decays, mean spectra of Auger and conversion electrons were generated for both AEE. These spectral data were used to determine the energy deposition in spherical volumes, uniformly filled with either I-123 or I-125 nuclides, by means of point kernel calculations.

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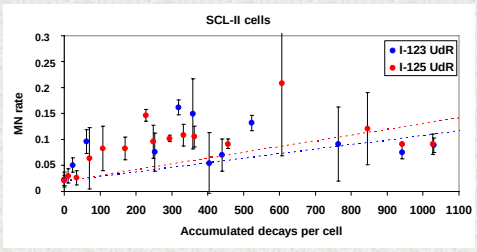
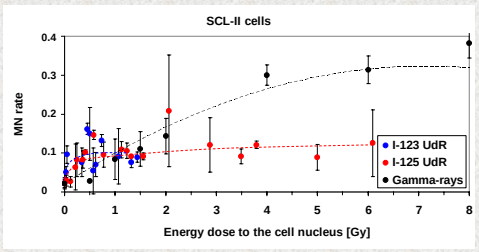
Methods

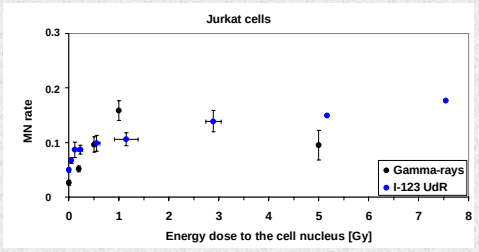
- Cytochalasin-B Micronucleus Assay was performed and Cytochlasin B concentration was optimized for each cell line. Automated MN detection and scoring was performed employing Metafer4/M-Search plus MN-Score software add-on (MetaSystems). Classifier were carefully adapted to each cell line. Each data point reflects at least 5000 scored cells in at least three independent experiments.
- Alkaline Comet Assay was used and automated comet analysis was performed using Metafer4/ CometScan (MetaSystems). Each data point reflects at least 300 Comets in at least three independent experiments.
- Cell cycle analysis was performed by flow-cytometry (BD CANTO II) using DNA-staining (Cytogreen) and the EdU-click-it assay. Synchronized SCL-II cells were co-labeled for 14 h with EdU and 0.1, 4 and 8 kBq/ml I-125-UdR. Fully labeled G2/M cells (pre-mitotic) as well as 1st, 2nd and 3rd division cells can be easily distinguished by EdU-signal intensity and DNA content. Cells were gated according to their EdU signal intensity: fully (= 100%) EdU-labeled G2/M cells were termed "pre-mitotic" cells, ~ 50 % EdU-labeled cells as "1st division" cells; ~20 % EdU-labeled cells as 2nd division cells and < ~ 10 % EdU-labeled as 3rd division cells.

Micronucleus Assay

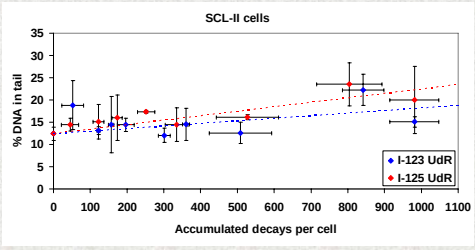


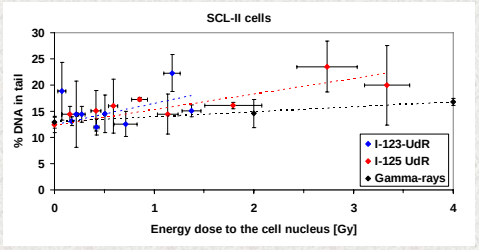


- I-123 UdR induced less micronuclei (MN) compared to I-125 UdR in respect to accumulated decays per cell (linear fitting of the data) in SCL-II cells.
- No differences between I-123 UdR and I-125 UdR can be observed when data are plotted as a function of energy dose to the cell nucleus.
- In the low dose range, I-123 UdR and I-125 UdR induced more MN in SCL-II and Jurkat cells when compared to external γ-irradiation (Cs-137, 0.7 Gy/min).
- Above 200 accumulated decays per cell, the dose-response curves of I-123 UdR and I-125 UdR showed a saturation of MN formation in both cell lines.



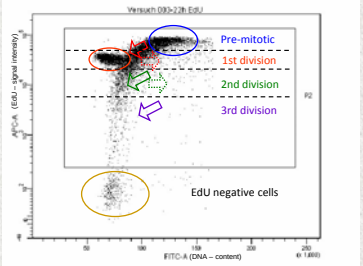
Comet Assay



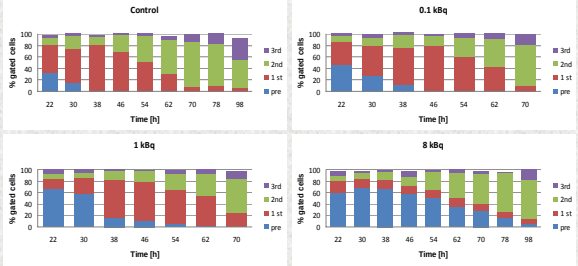


- I-123 UdR induced less chromatin damage in comparison to I-125 UdR in respect to accumulated decays per cell (linear fitting of the data).
- In terms of energy dose no differences between I-123 UdR and I-125 UdR can be observed.
- I-123 UdR and I-125 UdR induced more chromatin damage when compared to external γ-irradiation (Cs-137, 0.7 Gy/min).

Cell Cycle Analysis



- Synchronized SCL-II cells 22 h after EdU-click-labeling (non-irradiated control cells). Fully labeled G_2/M cells (blue circle, pre-mitotic) and 1st division G_1-cells (red circle) are easily distinguished by their DNA content and EdU-signal intensity. EdU negative cells (yellow circle) were excluded from analysis.



- 0.1 kBq/ml and 1 kBq/ml I-125 UdR induced a prominent G2/M arrest (pre-mitotic cells, blue bar) up to 38 h. At later time-points 1st division (red bar) and 2nd division (green bar) cells can be observed.
- 8 kBq/ml I-125 UdR induced a permanent G2/M-arrest (blue bars) because no increase in 1st division cells (red bar) is detectable. The 2nd division cells (green bar) are due to initially non-fully I-125-UdR labeled cells.