Proposal Code MD- 394
Proposal Title: IUdR synchrotron stereotactic radio therapy: mechanistic aspects.

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Aims of the experiment and scientific background

Heavy-atom-enhanced SSR is a new radiation therapy treatment that involves selective accumulation of high-Z elements in tumors, followed by stereotactic irradiation with x-rays from a synchrotron source. For instance in vitro studies have demonstrated that cells pre-treated with non-radioactive ^{127}IUdR had a higher sensitization factor than cells irradiated alone and that the optimal energy was 50 keV (Karnas 1999, Corde 2004). IUdR is known as an effective radiosensitiser, when it is incorporated in cellular DNA. Theoretical studies confirm that such an approach should be highly efficient at least if sufficient amounts of Iodine are incorporated in the nucleus (Karnas 2001, Moiseenko 2002).

Results

Experiments were performed on F98 cells grown in a medium enriched with IUdr. The amounts of incorporated IUdr were determined subsequently to DNA extraction and digestion by HPLC coupled to tandem mass spectrometry. Cells containing or not IUdr were then irradiated at either 50 or 33Kev, and the cell viability was assessed by measuring the ability of the cells to form colonies.
Unfortunately, due to an ESRF technical problem concerning the incubators, the study at 33.5 KeV was delayed one month later, and for that experiment the cells had incorporated lower amounts of IUdr and therefore a direct comparison of the results obtained for the two different energies is impossible.
Nevertheless, when about 2% of IUdr is incorporated into the DNA of F98 cells, compared to normal cells, a dose enhanced Factor (DEF) of 2 as determined by the clonogenic assay, confirming the radiosensitization effect of IUdr when incorporated into DNA. Interestingly, in addition to cell survival, radiation-induced DNA damage was also evaluated in irradiated cells using the comet assay allowing direct determination of the number of strand breaks. Again, when cells were grown in the presence of IUdr, an about 2 fold increase in DNA damage was observed as determined by the comet assay.
In conclusion, our results confirm the radiosensitization effect of IUdr when incorporated in the genomic DNA of growing cells, and confirm that iodine when incorporated into DNA is able to significantly increase the number of DNA damage induced by ionizing radiation. This indirectly suggests that DNA is the main target of ionizing radiation, at least when cell survival is used to evaluate the deleterious effect of radiation.
Additional work now is required to determine the influence of the energy of radiaton (33 versus 50 Kev) and to determine if the simultaneous use of IUdr together with contrast agent may enhance the DEF factor. This is of primary importance for improving the therapeutic efficacy of such an approach.