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Differences in correct and incorrect rejoining of DNA double-strand breaks in human fibroblasts having different radiosensitivity

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DNA double-strand breaks (DSBs) in irradiated cells are primarily responsible for the biological effects of ionizing radiation. The restitution of the broken ends depends on repair potential of the cells and determines their fate: survival, transformation or death. It has been suggested that differences in DSBs repair capacity between individuals and cultured cell strains may explain the differences in radiosensitivity observed in vivo and in vitro. We tested this hypothesis using two human primary fibroblast cultures the 1st having normal radiation-sensitivity (NRS) and the 2nd having hyper radiation-sensitivity (HRS) that was derived from a phenotypically normal pediatric patient treated for medulloblastoma with reduced doses consequent to a family history of hypersensitivity to radiation reminiscent of chromosomal fragility syndrome (Alsbeih et al. Radiother/Oncol 66(3), 2003).
Cell survival was determined by the clonogenic assay, chromosomal aberrations by FISH painting of chromosome 4, DSBs rejoining and fidelity by PFGE. Using Southern blotting, genomic DSBs rejoining was determined through the use of a probe for Alu repetitive sequence, while DSBs repair fidelity was measured in a 3.2 Mbp Not I restriction fragment on chromosome 21, with the probe D21S1 specific for that DNA fragment. NRS displayed normal radiosensitivity with a survival fraction at 2 Gy (SF2) of 0.35 while HRS was significantly more sensitive (SF2=0.15). HRS also incurred a higher level of chromosomal aberrations after 2 Gy than NRS. Residual genomic DSBs 24 h after 80 Gy were slightly higher in HRS compared to NRS. In both cells, however, this residual damage was small accounting for ≤ 10% of the initial damage in the whole genome. Measuring rejoining of correct and incorrect ends in the Not I restriction fragment revealed significantly higher misrejoining frequency in HRS when compared to NRS. The residual damage at 24 h was 10% and 40% of the initial damage (80 Gy) for NRS and HRS, respectively. Conclusions: differences in radiosensitivity are associated with differences in DSBs repair at low (chromosomal aberrations) and high radiation doses (PFGE). Measuring DSBs repair fidelity in specific regions of the genome could provide better resolution and a more accurate estimate of radiation-induced DNA damage. (KFSHRC work supported by KACST under LT-CNPSTI 9-MED749-20, RAC#2010 005; MDA work supported by NCI under CA06294).

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