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# Accumulation of non-DSB oxidative clustered DNA lesions in irradiated BRCA1 deficient cells affects mitigation of radiotoxicity and enhances chromosomal instability

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Radiation can increase significantly the level of oxidative stress that cell have to sustain and mitigate. Persistent of such stress can lead to unrepaired or misrepaired DNA lesions the accumulation of which is considered for many the initiation point for chromosomal instability, neoplastic transformation and human pathogenesis. Indeed, the presence of high oxidative stress in human patients or mice carrying BRCA1 mutations, in a homozygous or heterozygous form, is associated with a varying level of different lesion repair deficiencies, chromosomal instability, premature aging, high frequency of lymphoma, and ovarian or mammary tumour formation. In order to evaluate the role of BRCA1 deficiencies in the mitigation of radiation-induced toxicity and chromosomal instability we have used two human breast cancer cell lines, the BRCA1 deficient HCC1937 cells and as a control the BRCA1 wild type MCF-7 cells. Cell lines with DNA-PK repair deficiencies and peripheral blood lymphocytes from breast cancer patients with BRCA1/2 germ line mutations were also used. Repair of double strand breaks (DSBs), non-DSB bistranded oxidative clustered DNA lesions (OCDLs) and single strand breaks (SSBs) was measured in cells exposed to γ-ray doses (3-5 Gy). Given that radiosensitivity and chromosomal instability is related to accumulation of chromatid breaks, parallel experiments were performed in the induction of chromatid breaks after G2-phase irradiation by means of a standardized G2-assay that we have recently proposed. Independent monitoring of the γ-H2AX foci was also performed and metaphase chromatid lesions were measured as an indicator of chromosomal instability. HCC1937 cells were classified as highly radiosensitive since they showed a significant accumulation of OCDLs and chromatid breaks compared to MCF-7. BRCA1 partial expression contributed significantly in the overall repair of OCDLs. HCC1937 cells irradiated in plateau phase, surprisingly they demonstrated at metaphase a much higher level of unrejoined single chromatid lesions and a decreased yield of dicentrics chromosomes in comparison to the yields obtained in MCF-7 cells. Therefore, accumulation of OCDLs can lead to surviving cells with a high level of chromosomal aberrations and instability prone to transformation, suggesting a genuine role of BRCA1 in the mitigation of radiotoxicity, chromosomal instability and the development of breast cancer.

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