Premature Chromosome Condensation Reveals DNA-PK Independent Pathways of Chromosome Break Repair

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Cells of higher eukaryotes process double strand breaks (DSBs) in their genome using a non-homologous end joining apparatus that utilizes DNA-PK and other well characterized factors (D-NHEJ). Cells with defects in D-NHEJ, repair the majority of DSBs using a slow-repair pathway which is independent of genes of the RAD52 epistasis group and functions as a backup (B-NHEJ). Recent studies implicate DNA ligase III, PARP-1 and histone H1 in this pathway of NHEJ. The present study investigates the operation of B-NHEJ in the repair of interphase chromosome breaks visualized in irradiated G0 human lymphocytes by premature chromosome condensation (PCC). Chromosome breaks are effectively repaired in human lymphocytes, but repair is significantly compromised after treatment with wortmannin, a DNA-PK inhibitor. Despite slower kinetics, cells exposed to wortmannin rejoin the majority of ionizing radiation-induced chromosome breaks suggesting that B-NHEJ is also functional at the chromosome level. Complementation of D-NHEJ defect in wortmannin-treated lymphocytes by newly made DNA-PK is only possible under conditions of nuclear envelop break down and premature chromosome condensation, suggesting that in interphase cells the shunting of chromosome breaks from D-NHEJ to B-NHEJ is irreversible.

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