Genetic instability at low and high doses of contamination with 3H-Thymidine, comparison with external exposure to gamma-rays

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Radioactive compounds incorporated in tissues can have biological effects resulting from energy deposition in subcellular compartments. We addressed the genetic consequences of ^{3}H- or ^{14}C-thymidine incorporation into mammalian DNA. Low doses of ^{3}H-thymidine in CHO cells led to enhanced sensitivity compared with ^{14}C-thymidine. Compared with wild-type cells, homologous recombination (HR)-deficient cells were more sensitive to lower doses of ^{3}H-thymidine, but not to any dose of ^{14}C-thymidine. *XRCC4*-defective cells, however, were sensitive to both low and high doses of ^{3}H- and ^{14}C-thymidine, suggesting introduction of DNA double-strand breaks, which were confirmed by γ-H2AX foci formation. While γ-rays induced measurable HR only at toxic doses, sublethal contamination with ^{3}H- or ^{14}C-thymidine strongly induced HR. In comparison, at the same doses and at the same dose rates, γ-rays were much less efficient to induce HR. The stimulation level was in an inverse relationship to the relative contaminant energies. The RAD51 gene conversion pathway was involved as ^{3}H-thymidine induced RAD51 foci, and ^{3}H-thymidine-induced HR was abrogated by expression of dominant negative RAD51.

We then measured the impact of tritium contamination on cell cycle distribution. ^{3}H-thymidine induced a G2 block, which is sensitive to caffein and UCN01; moreover ataxia telangiectasia cells still retained the G2 block. These data suggest that the ATR pathway is involved in the response to ^{3}H-thymidine contamination.

Finally we measure ^{3}H-thymidine-induced mutagenesis. We show an increase in point mutations at low doses of contamination, followed by a decreased in mutation frequency. Mutagenesis appeared to result from oxydative stress since it was abolished by NAC treatment. Spectrum analysis of the mutation showed a complex spectrum. Finally induction of detoxifying genes and activities is consistent with our mutagenesis data. The data allowed us to propose a model for the cell response to low doses of ^{3}H-thymidine contamination.