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Reduction of Spontaneous Mutagenesis by Bystander Cell Death in V79 Cells

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Bystander responses have generated considerable interest in the field of modern radiobiology because of their non-liner relationship with low-dose radiation. Moreover, potential carcinogenic risks are considered to be increased by bystander responses because harmful consequences such as cell death and DNA damage typically induced in bystander cells.

Using the synchrotron X-ray microbeam irradiation system developed at the Photon Factory, KEK (Japan), we demonstrated that nitric oxide (NO)-mediated bystander cell death was biphasically enhanced in a dose-dependent manner. Here, we irradiated 5 nuclei of V79 cells (1.0×10^5 cells / dish) using 10 μm × 10 μm 5.35 keV X-ray beams. We measured the mutation frequency at the HPRT locus in bystander cells. The mutation frequency with the null radiation dose was 2.6 × 10^−5 (background level) that decreased to 5.3 × 10^−6 with a dose of approximately 1 Gy (dose absorbed by the nuclei of irradiated cells). At higher doses, the mutation frequency was the same as the background level. A similar biphasic dose response was observed for bystander cell death. Bystander cell death and HPRT mutation frequency were significantly correlated ($p < 0.05$). The correlation between these responses indicated that bystander cell death and mutagenesis in bystander cells were responses to the same or related stimuli.

Oxidative damage of nucleotides by reactive oxygen species (ROS) is thought to play an important role in spontaneous mutagenesis. Intracellular ROS levels are known to be persistently high in genetically unstable cells because these cells have low antioxidative activity. Further, a recent study showed that exposure to NO causes mitochondrial degeneration and subsequent cell death in cells with low antioxidative activity. Thus, we hypothesize that genetically unstable cells might be selectively killed by bystander responses because of their low antioxidative activity, given that NO is an important mediator of bystander cell death. As a result, the antioxidant ability of the surviving cell population may have increased, and hence, mutagenesis may have been suppressed in the bystander cells.

Our results suggested that radiation-induced bystander responses can enhance the selective killing of genetically unstable cells in the bystander cell population and that this selective cell death might act as a protective mechanism against increases in non-lethal, potentially carcinogenic damage, e.g., mutations.

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