Low-dose high-LET heavy ion-induced bystander signaling

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The radiation-induced bystander response (RIBR) is a cellular response induced in nonirradiated cells that receive bystander signals from directly irradiated cells within an irradiated cell population.[1)] The RIBR induced by low doses of high-LET radiations is an important issue concerning the health of astronauts and in heavy-ion radiation cancer therapy. Here, we investigated the molecular mechanisms underlying and biological implications of the RIBR induced by such low doses of high-LET radiations.

Figure 1 shows the clonogenic survival curve of normal human fibroblast WI-38 cells irradiated with Fe ions (1000 keV/μm). Cells were harvested from the cell culture flask immediately (0 h) or 16–24 h after irradiation, and the surviving fraction was determined by using a colony formation assay. At doses below 0.2 Gy, the surviving fractions of the cells harvested 16-24 h after exposure to Fe ions were much lower than those extrapolated from higher doses above 0.1 Gy using the linear-quadratic model (LQ model).[2)] On the other hand, the cells harvested immediately after exposure did not show such a high cell killing effect at lower doses. These results suggest that an adequate incubation period is necessary for the bystander signal induction and transfer.

Previously, we have reported that reactive oxygen species (ROS), gap-junction intercellular communication (GJIC), and cyclooxygenase-2 (COX-2) protein as well as nitric oxide (NO) may be involved in high-LET radiation-induced bystander signal transfer.[3)] Here, we show the progress of results reflecting new data [Fig. 2]. Lindane and NS-398 (an inhibitor of GJIC and COX-2, respectively) were dissolved in DMSO (a scavenger of ROS). DMSO did not significantly suppress the bystander cell killing effect. In contrast, lindane, NS-398, and c-PTIO (a scavenger of NO) significantly suppressed cell death to similar levels. Cells pretreated with both c-PTIO and lindane did not show significantly higher surviving fraction than those pretreated with lindane or c-PITO alone. These results suggest that bystander signaling through GJIC and the cell culture medium induces the bystander cell killing effect in a coordinated manner.

Currently, we are examining the role of the NF-κB/Cox-2/prostaglandin E2 and NF-κB/iNOS/NO pathways,[4)] which may be activated in bystander cells.

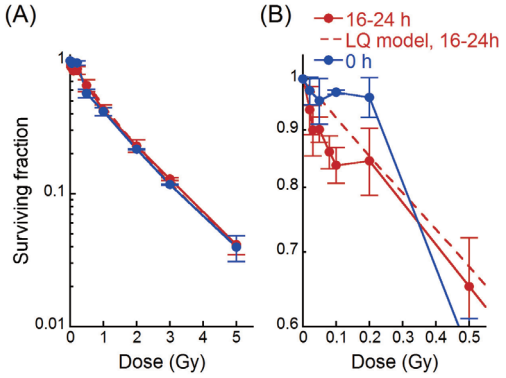

Fig. 1. Survival curves of WI-38 cells. Confluent monolayers of WI-38 cells were irradiated with 90 MeV/u Fe ions (1000 keV/μm) and the cells were harvested immediately (0 h) or 16–24 h after irradiation. The surviving fraction was determined by using a colony forming assay. Panel A shows all data obtained in this study. Panel B shows surviving fractions at doses below 0.5 Gy. The error bars represent the standard deviations.

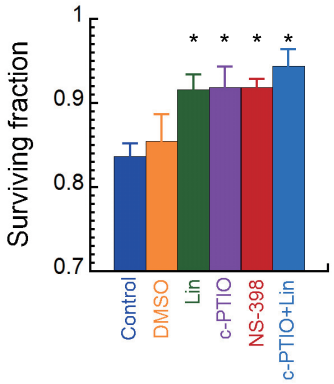

Fig. 2. Effect of inhibitors or scavengers. DMSO (0.1%), lindane (Lin, 50 μM), c-PTIO (20 μM), or NS-398 (50 μM) was added to the medium 2 h before irradiation.[5)] WI-38 cells were irradiated with 0.1 Gy Fe ions. The error bars represent the standard errors of the mean (SEM) (n=3–4).*$P < 0.05$, for comparison with irradiated control cultures.

References

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