Cell-killing effect of low doses of high-LET heavy ions (VI)

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Non-DNA-targeted effects are not a direct consequence of radiation-induced initial lesions produced in cellular DNA, but are an indirect consequence of intra- and intercellular communications involving both irradiated and nonirradiated cells. These effects include low-dose hyper-radiosensitivity (HRS) and radiation-induced bystander response (RIBR).[1,2] RIBR is a cellular response induced in nonirradiated cells that receive bystander signals from directly irradiated cells within an irradiated cell population.[1,2] 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 RIBR induced by such low doses of high-LET radiations. We previously found that HRS was induced in normal human fibroblast WI-38 cells that were irradiated with low doses of high-LET argon (Ar) and iron (Fe) ions, suggesting that RIBR was induced.[3–5] Nitric oxide (NO) was found to be involved in this process.[3–5] Furthermore, we found that reactive oxygen species (ROS), gap-junction intercellular communication (GJIC), and cyclooxygenase-2 (COX-2) protein as well as NO may be involved in Ar-ion-induced bystander signal transfer.[4] Here, we examined the effects of a scavenger of ROS (DMSO) and an inhibitor of GJIS (lindane) or COX-2 (NS-398) on Fe-ion-induced RIBR.

Here, we have shown the revised clonogenic survival curve of WI-38 cells irradiated with Fe ions; the curve was obtained by adding new data to previous results[3] [Fig.1]. HRS could be clearly observed in cells irradiated with Fe ions at doses lower than 0.2 Gy and was partly suppressed by pretreatment with carboxy-PTIO (c-PTIO), an NO scavenger.

Next, we examined HRS suppression at 0.1 Gy by DMSO, lindane, c-PTIO or NS-398 pretreatment [Fig. 2]. Lindane and NS-398 were dissolved in DMSO. DMSO did not significantly suppress the HRS, although the standard errors of the mean (SEM) were large. In contrast, lindane, NS-393, and c-PTIO significantly suppressed HRS to similar levels. These results suggested that the GJIC and COX-2 mediated pathway as well as NO was also involved in Fe-ion-induced bystander signal transfer. Currently, we are examining the role of the NF-κB/Cox-2/prostaglandin E2 and NF-κB/iNOS/NO pathways,[2] which may be activated in bystander cells that have been subjected to ROS and NO, in HRS induced by high-LET radiations.

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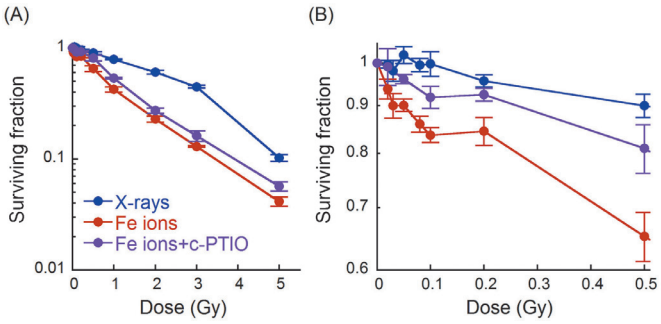

Fig. 1. Cell-survival curves of WI-38 cells. Confluent monolayers of WI-38 cells were irradiated with 90 MeV/u Fe ions (1000 keV/μm) and some of the cells were pretreated with c-PTIO (20 μM). The surviving fraction was determined by a colony forming assay. The error bars represent the standard error of the mean (SEM) (n=3-5).

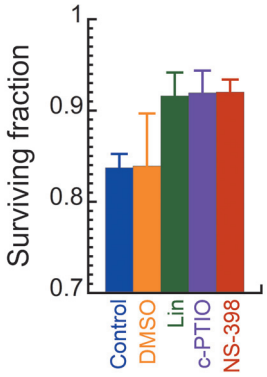

Fig. 2. Effect of inhibitors or scavengers. DMSO (0.1%), lindane (Lin, 50 μM), c-PTIO (20 μM) or NS-398 (50 μM) was added to the medium 2 h before irradiation.[6] WI-38 cells were irradiated with 0.1 Gy Fe ions. The error bars represent the standard error of the mean (SEM) (n=3-4).

References

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