

## THE ROLES OF SUPEROXIDE DISMUTASE (SOD) IN LOW DOSE RADIATION INDUCED ADAPTIVE RESPONSE

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### Background:

The potential risks of exposure to low dose radiation are of major concerns to the DOE/OBER Low Dose Radiation Research Program. It has been long recognized that much of the radiation-induced genetic damage to cells are caused by secondary oxidative species. Therefore internal cellular defense systems against oxidative stress play significant roles in countering genetic damage induced by ionizing radiation. The role of the detoxifying enzymes may be even more prominent in the case of low-dose, low-LET irradiation, as the majority of genetic damage may be caused by secondary oxidative species. In this study we attempted to decipher the roles of the superoxide dismutase (SOD) genes, which are responsible for detoxifying the superoxide anions. In particular, we studied their involvement in adaptive response, whereby an initial low dose radiation induced biological processes that are protective to the damaging effects of a second, higher level radiation insult.

### Approach:

In order to study the roles of SOD genes in low-dose radiation-induced adaptive response, we used a combination of **RNA interference (RNAi or siRNA)**, **adenovirus-mediated gene transduction**, and **chemical mimetic strategies** to regulate the activities of SOD. We quantified genetic damage caused by higher doses of radiation after an initial exposure of the cells to an initial low dose of (0.1 Gy) of X-radiation in a immortalized human epithelial cell line. The micronucleus assay was used to quantify the extent of DNA damage in the irradiated cells.

### Results:

Our initial results indicated that low dose (10 cGy) irradiation has minimal effect on micronucleus generation in RPE (retinal pigment epithelial) cells. In contrast, high dose (3 Gy) radiation has a significant effect on micronucleus (MN) generation in RPE cells, increasing the background frequency of MN 5 fold over background. Consistent with previous reports, a small (10 cGy) priming dose 5 hours prior to the 3 Gy irradiation significantly reduced radiation induced MN (by >60 %). The adaptive response is correlated with a significant reduction in level of free radical generation as measured by a fluorescent probe approach. Furthermore, the addition of a novel Mn-Porphyrin, which is a novel SOD mimetic, significantly reduced MN induction by radiation. In addition, we found that the low-dose radioadaptive response is critically dependent on the function of the SOD2 gene. Blocking the SOD2 function through siRNA abolished the adaptive response in the RPE cells.

### Conclusion:

Our results clearly indicate that low dose radiation induces an adaptive response in mammalian cells and reactive oxygen species and the superoxide dismutases play essential roles in this radioadaptive response.

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