NFκB in the Thiol-Induced Adaptive Response (B)

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Activation of the transcription factor NFκB in response to stress including exposure to ionizing radiation propagates a cascade of complex signaling pathways. One of the pathways involves the elevation of manganese superoxide dismutase (SOD2) and the subsequent over expression of genes associated with the adaptive response. SOD2 is a mitochondrial matrix metalloprotein that catalyzes the dismutation of superoxide radicals produced by a variety of agents including ionizing radiation. To characterize the role of SOD2 in the radiation- and thiol-induced adaptive responses, wild type mouse embryo fibroblasts (wtMEF) and MEF tumor necrosis factor receptor 1 and 2 negative (double knockout cells, $MEF_{TNFR1^-/TNFR2^-}$) were exposed to 10 cGy x-rays or 40 μM WR1065 followed 24 hr later by 2 Gy-x rays. Reproductive integrity ("cell survival") and micronuclei damage were used to evaluate the effectiveness of pretreatments with radiation and the thiol. Exposure of wtMEF and $MEF_{TNFR1^-/TNFR2^-}$ cells to 2 Gy resulted in a significant increase in the mean number of micronuclei observed relative to unirradiated control cells. However, when wtMEF cells were treated 24 hr earlier with 10cGy or WR1065 before the 2 Gy challenge dose, the frequencies of micronuclei formation were significantly reduced compared to wtMEF cells not pretreated and cell survival levels of wtMEF cells was significantly increased. The adaptive response for $MEF_{TNFR1^-/TNFR2^-}$ cells stand in stark contrast to the results previously presented. The double knockout MEF cells showed no evidence of an adaptive response if exposed to 10 cGy of ionizing radiation 24 h prior to a 2Gy challenge for elevated cell survival and only a marginal protection against micronuclei formation. Interestingly, exposure of these cells to 40 μM WR1065 resulted in an adaptive protective effect suggesting that the thiol effect is downstream of TNF signaling. It is proposed that TNFα signaling plays an important role in the low dose radiation induced adaptive response and that TNFR mediated pathways play a role in whether cells exhibit either an enhanced or reduced resistance to ionizing radiation. An important downstream transcription factor affected by TNFα mediated signaling is nuclear transcription factor κB (NFκB). It is further proposed that the thiol-induced adaptive response is mediated by direct activation of NFκB which then leads to elevated SOD2 gene expression and subsequent elevated SOD2 enzymatic activity in the mitochondria. SOD2 is an important mediator of both adaptive responses as demonstrated by the abilities of SOD2 antisense and siRNA exposures to completely inhibit these effects.

This work was supported by DOE grant DE-SC0001271 (D.J.G.).