Molecular Targets for Radioprotection by Low Dose Radiation Exposure

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Adaptive response is a reduced effect from a higher challenging dose of a stressor after a smaller inducing dose had been applied a few hrs earlier. Radiation induced fibrosarcoma (RIF) cells did not show such an adaptive response, i.e. a reduced effect from a higher challenging dose (2 Gy) of a radiation after a priming dose (1 cGy) had been applied 4 or 7 hrs earlier, but its thermoresistant clone (TR) did. Since inducible HSP70 and HSP25 expressions were different between these two cell lines, the role of inducible HSP70 and HSP25 in adaptive response was examined. When inducible hsp70 or hsp25 genes were transfected to RIF cells, radioresistance in clonogenic survival and reduction of apoptosis was detected. The adaptive response was also acquired in these two cell lines, and inducible hsp70 transfectant showed more pronounced adaptive response than hsp25 transfectant. From these results, inducible HSP70 and HSP25 are at least partly responsible for the induction of adaptive response in these cells. Moreover, when inducible HSP70 or HSP25 genes were transfected to RIF cells, co-regulation of each gene was detected and heat shock factor (HSF) was found to be responsible for these phenomena.

In continuation of our earlier study on the involvement of heat shock protein (HSP) 25 and HSP70 in the induction of adaptive response, we have now examined the involvement of these proteins in the induction of the adaptive response, using an animal model system. C57BL6 mice were irradiated with 5 cGy of gamma radiation 3 times for a week (total of 15cGy) and a high challenge dose (6Gy) was given on the day following the last low dose irradiation. Survival rate of the low dose pre-irradiated mice was increased to 30%. Moreover, high dose-mediated induction of apoptosis was also reduced by low dose pre-irradiation. To elucidate any link existing between HSP and induction of the adaptive response, reverse transcriptase (RT)-polymerase chain reaction (PCR) analysis was performed using splenocytes. High dose radiation up-regulated the expression of HSP25 and especially HSP70; while expression of other HSPs such as HSC70, HSP90, and B-crystalline did not change. When splenocytes from HSP70 transgenic mice were pre-irradiated with a low dose of radiation, a reduction in cell death by high dose radiation was observed. These results, suggest that HSP70 is a key molecule in radioprotective effect by low dose radiation.