A role for c-Abl/p53 pathway in radio-adaptive response

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The radio-adaptive response, i.e. a low dose of radiation can protect cells and organisms from the effects of a subsequent higher dose, is a phenomenon that has been widely recognized. However, mechanisms underlying such radiation hormesis remain largely unclear. Using human normal lymphocytes cultured at physiological oxygen pressure (5%), we observed that cells treated with a priming dose (10 cGy) of radiation exhibited a faster kinetics of disappearance of pH2AX induced by a subsequent challenge dose of 4 Gy when compared with cells treated with the challenge dose only. At 2-hour following irradiation at 4 Gy, there were approximately 3 to 5 folds more pH2AX detected in cells treated with the challenge dose only than cells treated with the priming and challenge doses. Together with the data that a comparable level of pH2AX was seen at 30 min post-irradiation with 4 Gy in both groups, the results suggest that treatment of cells with the priming dose stimulates the process of pH2AX removal, indicative of DNA repair. To gain an understanding of the priming dose-induced DNA repair, we examined the cell cycle progression, considering the fact that DNA repair and cell cycle are tightly coupled. Analysis of BrdU incorporation detected a greater S phase population in cells treated with priming and challenge doses over cells treated with the challenge dose only, indicating a lesser extend of G1 cell cycle arrest in priming plus challenge doses treated cells. It has been well-documented that cells in S phase usually repair DNA damages most efficiently relative to cells in other cell cycle phase. Our data seems to be in line with such a correlation. We next went on to explore the mechanisms underlying the priming dose of IR-induced cell cycle progression. Recognizing the critical role of p53 in IR-induced cell cycle checkpoint, we examined the p53 response. Interestingly, we observed a moderate decrease of the p53 protein abundance in priming dose-treated cells. Moreover, the p53 level was found significantly lower in priming plus challenge doses than challenge dose only treated cells, implicating an involvement of p53 in the radio-adaptive response. The critical role of p53 in the radio-adaptive response was confirmed by using pared MEFs isolated from either p53-null mice or the wild type littermates. Collectively, our data with in vitro cell cultures suggests a novel function of p53 in regulation of radio-adaptive response. To test the in vivo relevance of the observation, we compared p53(172H) knockin mutant mice (obtained from Dr. Lozano from MD Anderson Cancer Center) with its wild type littermate. While confirmation is required, preliminary data derived from the mouse experiments seemed to be consistent with the in vitro result, implicating p53 in radio-adaptive response.

In light of the findings that both c-Abl deficient as well as p53 deficient cells showed impaired radio-adaptive response, we are exploring the functional interaction c-Abl with the p53 pathway in regulation of the radio-adaptive response. Pilot experiments showed that c-Abl phosphorylates both MDM2 and MDMX, two negative regulators of p53, suggesting a possibility that c-Abl regulates p53 by modulating the activity of MDM2/MDMX. Preliminary results suggest that c-Abl promote MDM2/MDMX-mediated p53 degradation in a kinase-dependent manner, implicating a potential mechanism underlying the priming dose IR-induced down regulation of p53. We are currently confirming the results. If verified, c-Abl tyrosine kinase-mediated p53 regulation may represent a novel pathway involved in radiation adaptive response (This work is supported by DOE 110976).