

135 The phosphatidylinositol 3-kinase, inhibited by low dose of wortmannin, affects radiation sensitivity

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It was already reported that high dose of wortmannin (10-100  $\mu\text{M}$ ) inhibits DNA-PK or ATM and sensitizes to X ray irradiation. But there is no report about the intrinsic phosphatidylinositol 3-kinase, inhibited by low dose wortmannin, may affect radiation sensitivity or not. We investigated about the role of phosphatidylinositol 3-kinase for radiation sensitivity using low dose of wortmannin (lower than 1  $\mu\text{M}$ ). Low dose of wortmannin enhanced radioresistance in A172 cells (human glioblastoma, wild-type p53) but did not show significant enhancement of radioresistance in T98G cells (human glioblastoma, mutant p53). This indicates that the phosphatidylinositol 3-kinase may affect radiosensitivity through p53 pathway.

136 Possible involvement of DNA-PK in restoration of mutant p53 to normal p53 activity by glycerol after X-ray irradiation

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We previously reported that glycerol was effective in restoring mutant p53 (mp53) to normal p53 function leading to normal *WAF1* expression after heat or X-ray stress in human glioblastoma cells. We report whether DNA-PK contributes to restoration of mp53 to normal p53 activity by glycerol after X-ray irradiation. *WAF1* expression was hardly induced after treatment by X-ray or glycerol alone treatment in mp53-transfected A-172 cells but the combined treatment of X-ray and glycerol apparently induced *WAF1* expression. By the addition of wortmannin (20  $\mu\text{M}$ ), the *WAF1* accumulation was suppressed after the combined treatment. Gel mobility-shift assay showed DNA binding activity of p53 increased *in vivo* system of cultured cells treated with X-ray and glycerol, but not in *in vitro* system of nuclear extracted from intact cells. These results suggested that DNA-PK involved in X-ray-induced p53-dependent signal transduction pathway plays an important role in restoration of mp53 to normal p53 by glycerol after X-ray irradiation.

137 Cyclin-Dependent Kinase 2 Activity after X-irradiation of Apoptosis-Sensitive and -Resistant Mouse Lymphoma Cell Lines

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Previous reports have indicated that X-rays cause apoptotic cell death of thymus-derived cells *in vitro* and *in vivo*. It is important to understand the signaling events that control this process. In X-irradiated mammalian cells, certain checkpoint pathways are activated via certain cell cycle molecules and this signals may play an important role in cellular responses evoked by X-rays. Therefore, we examined whether cyclin-dependent kinase 2 (Cdk2), an important checkpoint regulator for cell cycle progression through interphases, is activated during thymic apoptotic processes after X-irradiation. Apoptotic cell death was observed in apoptosis-sensitive thymic lymphoma cells (p53+/+ cells) when exposed to over 0.5 Gy of X-rays and concomitantly Cdk2 kinase activity increased. In contrast, such a post-irradiated increment of Cdk2 activity was not observed in apoptosis-resistant thymic lymphoma cells (p53-/- cells). These results suggest that thymic cells may utilize Cdk2 to mediate death signaling resulting from X-irradiation.