Translationally Controlled Tumor Protein Protects against DNA Damage in Low Dose γ-Irradiated Cells

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We have previously shown that exposure to low dose/low dose rate γ-rays can protect normal human and rodent cells against oxidative/clastogenic damages induced spontaneously or by a subsequent challenge dose of ionizing radiation. To gain insight into the mechanisms underlying these effects, we used amine-specific isobaric tags for relative and absolute quantitation (iTRAQ)-based approach to identify induced proteolytic events. Intriguingly, the Translationally Controlled Tumor Protein (TCTP) was significantly up-regulated after 10cGy (0.2cGy/h) but not after 4 Gy (1 Gy/min) in several strains of normal human fibroblasts maintained in 2- or 3-dimensional architecture and in tissues of mice exposed to ^{137}Cs γ-rays. TCTP is highly conserved and is abundantly expressed in many eukaryotes, but its role in radiation effects is poorly understood. Whereas low dose γ-rays stabilized TCTP, high doses enhanced its degradation. TCTP levels were increased by 2-fold in cells exposed to doses as low as 1cGy. Cell fractionation studies showed that in nuclei, TCTP is increased by ~9-folds. Strikingly, knockdown of TCTP expression by siRNA abolished the low dose γ-ray-induced protective effect against chromosomal damage, and highlighted a role for TCTP in DNA repair. This was supported by a decrease, in cells treated with TCTP siRNA, in the activity of ku70 and ku80 that are important components of DNA repair. Knockdown of TCTP expression did not alter repair of chromosomal damage in high dose-irradiated cells. We also show that TCTP regulation by low dose γ-rays is dependent on ATM, and does not require p53 or HDM2. Together, our results suggest a novel role of TCTP in protective effects against DNA damage, radiation-induced p53 signaling and the G_1 checkpoint. They reveal the complexity of low dose radiation effects, and indicate that low dose effects may not be universally extrapolated from effects observed at high doses.

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