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TP53INP1 gene is implicated in radiation-induced senescence

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BACKGROUND AND PURPOSE: Tumor protein 53-induced nuclear protein-1 (TP53INP1) encodes two nuclear protein isoforms (TP53INP1□ and TP53INP1□) and transcription is activated by p53. Overexpression of TP53INP1 promotes apoptosis and cell cycle arrest in different tumor cell lines. Therefore, TP53INP1 appears as a key element in p53-mediated cell death and cell cycle arrest, induced by cellular stress. Moreover, it was shown that TP53INP1 interacted with p53 and these interactions modified the transcriptional activity of p53 on several target genes such as CDKN1A, PIG-3 and MDM2. The objective of this study was to assess whether TP53INP1 plays a functional role in regulating cellular responses to IR.
METHODS: F11hTERT (telomerase immortalized) human fibroblast cells were used in the study. To investigate the role of TP53INP1 in radiation response the gene was silenced by the stable transfection of shRNAs using lentiviral vectors. Cells were irradiated direct and bystander effects were assessed by following survival using colony-forming assay and by investigating mitochondrial DNA deletions by quantitative real time PCR Alterations in cell cycle distribution were analyzed by flow cytometry, while radiation-induced senescence was studied with SA-□-Gal staining. Autophagy changes were measured by Acridine Orange staining and the expression of TP53INP1, GDF-15, GADD45A and CDKN1A was measured by real-time PCR.
RESULTS: We demonstrate here that IR results in dose dependent expressional changes of TP53INP1 in both irradiated and bystander fibroblast cells. We constructed stable fibroblast cell lines in which the expression of TP53INP1 was constitutively knocked-down by RNA interference. TP53INP1 was required for IR induced maximal elevation of CDKN1A and GDF-15 expressions. Likewise, autophagy and senescence was deregulated following irradiation in the absence of TP53INP1. TP53INP1 deficient cells showed resistance of the G2-delay, and the proliferation rate was higher compared with wild type F11hTERTcells. Finaly, we showed that TP53INP1 proficiency is important for clonogenic survival after radiation.
CONCLUSIONS: These data reveal novel functional roles for TP53INP1 in cell cycle, survival and responses to IR. Taken together, we concluded that autophagy impairment induces premature senescence through a TP53INP1-dependent manner in primary human fibroblasts.

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