Abstract

p53 is an important mediator of the cellular stress response with roles in cell cycle control, DNA repair, and apoptosis. 53BP2, a p53-interacting protein, enhances p53 transactivation, impedes cell cycle progression, and promotes apoptosis through unknown mechanisms. We now demonstrate that endogenous 53BP2 levels increase following UV irradiation induced DNA damage in a p53-independent manner. In contrast, we found that the presence of a wild-type (but not mutant) p53 gene suppressed 53BP2 steady-state levels in cell lines with defined p53 genotypes. Likewise, expression of a tetracycline-regulated wild-type p53 cDNA in p53-null fibroblasts caused a reduction in 53BP2 protein levels. However, 53BP2 levels were not reduced if the tetracycline-regulated p53 cDNA was expressed after UV damage in these cells. This suggests that UV damage activates cellular factors that can relieve the p53-mediated suppression of 53BP2 protein. To address the physiologic significance of 53BP2 induction, we utilized stable cell lines with a ponasterone A-regulated 53BP2 cDNA. Conditional expression of 53BP2 cDNA lowered the apoptotic threshold and decreased clonogenic survival following UV irradiation. Conversely, attenuation of endogenous 53BP2 induction with an antisense oligonucleotide resulted in enhanced clonogenic survival following UV irradiation. These results demonstrate that 53BP2 is a DNA damage-inducible protein that promotes DNA damage-induced apoptosis. Furthermore, 53BP2 expression is highly regulated and involves both p53-dependent and p53-independent mechanisms. Our data provide new insight into 53BP2 function and open new avenues for investigation into the cellular response to genotoxic stress.