UV but not γ Irradiation Accelerates p53-induced Apoptosis of Teratocarcinoma Cells by Repressing MDM2 Transcription

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ABSTRACT

Induction of p53 by DNA damage results in apoptosis of teratocarcinoma cells, whereas MDM2, encoded by a p53-responsive gene, can reverse this phenotype by inhibiting p53 function. Here we report that UV (10 or 20 J/m²), but not γ irradiation (7 or 10 Gy), caused a massive apoptosis of human teratoma Tera-2 or murine testicular carcinoma F9 cells, both of which contain wild-type p53, but not murine p53 null testicular carcinoma EB-16 cells. Most Tera-2 or F9 cells died overnight after UV but not γ irradiation. Correlated with this phenotype was a dramatic and continuing accumulation of p53 proteins after UV but not γ irradiation. This was attributable to UV-responsive repression of MDM2 expression, because both its protein and RNA were not detectable after UV irradiation. This UV-induced repression appeared to be specific to MDM2, because expression of other genes, such as p21, p53, or glyceraldehyde-3-phosphate dehydrogenase, was not reduced. Also, RNase protection analysis showed that a DNA region, excluding the p53 binding site, in the MDM2 promoter mediated transcriptional repression in response to UV. Thus, these results suggest that UV but not γ irradiation can induce p53 by suppressing MDM2 expression in a p53-independent fashion and subsequently, massive cell death.

INTRODUCTION

The tumor suppressor p53 protein is a crucial player in preventing cells or tissues from undergoing transformation or tumorigenesis. Thus, this protein is tightly regulated by multiple mechanisms. In response to a variety of DNA-damaging signals including UV or γ irradiation, p53 is up-regulated, and its protein and activity levels are dramatically induced, subsequently leading to apoptosis and/or cell growth arrest (1, 2). Recent studies suggest that UV and γ irradiation appear to activate p53 through distinct pathways (3–12).

Upon activation, p53 transcriptionally turns on a number of downstream target genes, most of which mediate p53-dependent apoptosis or growth arrest (1, 2). However, one of these target genes encodes a protein that negatively controls p53 function (MDM2 (13), which is encoded by the mdm2 oncogene amplified on a mouse double-minute chromosome in the 3T3DM cell line (14). This gene is amplified or overexpressed in approximately one-third of human sarcomas (15, 16), in which mutation of p53 has not yet been reported (17). The tumorigenic potential of MDM2 is closely linked to its ability to inhibit the growth suppression function of p53 (13). Deletion of the mdm2 gene is lethal to mice, whereas further disrupting the p53 gene rescues the mdm2 null mice, and therefore, MDM2 is a physiological regulator of p53 (18, 19). MDM2 affects both p53 stability and activity. It binds to the NH₂-terminal domain of p53, inhibits p53-dependent transcription (20), and also enhances the ubiquitination (21) and proteolytic degradation of p53 (22, 23), hence forming a unique autoregulatory negative feedback loop for monitoring p53 functions (24).

Interestingly, cells also develop mechanisms that can induce p53 by blocking the MDM2 negative feedback loop. For instance, the aforementioned serine 20 phosphorylation in response to γ irradiation interrupts the interaction of MDM2 with p53 and hence limits its chance to degrade the p53 protein (8, 9). Also, an MDM2-binding miniprotein was shown to suppress the negative effect of MDM2 on p53 (25). Moreover, the mouse tumor suppressor p19atf (p14arf for the human protein) was shown recently to bind to MDM2 and to suppress its degradation effort on p53 (26–30), thus leading to activation of p53. Oncoproteins, such as Myc, E1A, or Ras, can activate p53 by inducing p19arf and thus abrogating the MDM2-mediated p53 degradation (26, 31–33). Hence, interfering with the MDM2-p53 feedback loop is important for p53 activation. In this study, we describe a different mechanism responsible for disrupting the MDM2-p53 circuit. We found that in response to UV-caused but not γ-induced DNA damage, expression of MDM2 at both RNA and protein levels was dramatically reduced in human and mouse teratocarcinoma cells. Correspondingly, the level of p53 protein increased remarkably and constantly only in the UV-irradiated cells, whereas induction of p53 in γ-irradiated cells displayed a two-peak pattern, consistent with previous reports (6, 34). Consequently, cells after UV but not γ irradiation underwent a massive apoptosis that is dependent on p53. In agreement with these results was that the UV-responsive DNA cis element mediating transcription repression was detected in the non-p53RE region of the MDM2 promoter. These results suggest that in cells, there may be an UV-responsive cellular mechanism (component) that can suppress expression of MDM2 and thus result in a remarkable increase of p53.

MATERIALS AND METHODS

Reagents and Buffers. Trizol reagent was purchased from Life Technologies, Inc. Western blotting lysis buffer is composed of 50 mM Tris/HCl (pH 8.0), 0.5% NP40, 5 mM EDTA, 2 mM DTT, 150 mM NaCl, and 0.2 mM phenylmethylsulfonyl fluoride. SNNTGE is composed of 50 mM Tris/HCl (pH 7.4), 5 mM EDTA, 1% NP40, 500 mM NaCl, and 5% sucrose. RIPA is comprised of 50 mM Tris/HCl (pH 7.4), 150 mM NaCl, 1% Triton X-100, 0.1% SDS, and 1% (w/v) sodium deoxycholate. Immunoprecipitation-kinase lysis buffer is 100 mM HEPES-KOH (pH 7.4), 2 mM EGTA, 50 mM β-glycerophosphate, 10% glycerol, and 1% Triton X-100. LiCl buffer is 500 mM LiCl, 100 mM Tris/HCl (pH 7.6), and 0.1% Triton X-100. SSC (20x) solution is composed of 3 M NaCl and 0.3 mg sodium citrate (pH 7).

Plasmids and Antibodies. PCDNA-p21, pCDNA-MDM2, and pCDNA-p53 plasmids encoding mouse p21, MDM2, and p53, respectively, were gifts from Matt Thayer (Vollum Institute, Portland, OR). Cosx1-CAT, H5.0-CAT, BP100-CAT, or H0.5DA-CAT, driven by different DNA fragments of the MDM2 first intron promoter as illustrated in Fig. 6, were generously provided by Xiangwei Wu (Institute of Aging at Baylor Medical College, Houston, TX) and derived from the 1634-CAT plasmid containing the TATA and Inr motifs from the adenovirus major late promoter, as described (24). Polyclonal anti-MDM2 and monoclonal anti-p53 Pab421 antibodies were as described (35).

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3 The abbreviations used are: CAT, chloramphenicol acetyltransferase; WB, Western blot; GAPDH, glyceraldehyde-3-phosphate dehydrogenase.
and incubated with 32P-labeled cDNA probes encoding mouse p53, p21, loaded onto a 1.5% agarose gel and transferred to a nitrocellulose membrane. F9 or Tera-2 cell and nuclear extracts were prepared as described (37). and Tera-2 cells contain wild-type p53, whereas EB-16 cells are p53 free (36). sodium pyruvate was used for murine testicular carcinoma F9 or EB-16 cells. F9 analysis, as described below.

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Fig. 1. Morphology of F9 cells after irradiation. F9 cells (50% confluent) were exposed to UV (20 J/m²), γ-ray (10 Gy), or 10 μm etoposide, as indicated. Cells were examined and photographed under light microscope at the 4 × 25 zoom 24 h after irradiation. The exact same phenotype was also observed with Tera2 cells.

Monoclonal anti-p21 antibodies were purchased from Santa Cruz Biotechnology, Inc. (Santa Cruz, CA).

Cell Lines and Cell Culture. Human teratoma tera-2 cells were cultured in DMEM supplemented with 10% fetal bovine serum, 50-units/ml penicillin, and 0.1-mg/ml streptomycin at 37°C in a 5% CO₂ atmosphere. DMEM without sodium pyruvate was used for murine testicular carcinoma F9 or EB-16 cells. F9 and Tera-2 cells contain wild-type p53, whereas EB-16 cells are p53 free (36).

Preparation of F9, Tera-2, or EB-16 Whole-Cell and Nuclear Extracts. F9 or Tera-2 cell and nuclear extracts were prepared as described (37).

UV and γ irradiation of Culture Cells. Cells were irradiated with UV (10 or 20 J/m²) using the 254-nm source of a UV transilluminator (UVP, Inc., Upland, CA) or γ-ray (dose as indicated in figure legends), as described (6, 38). After irradiation, cells were harvested either at different time points as indicated in the figures or 8 h afterward for Western blot or Northern blot analysis, as described below.

WB Analysis. WB analysis was performed as described (35). Proteins from cell lysates (100 μg) of the irradiated or nonirradiated cells were separated by SDS-PAGE and transferred to nitrocellulose membrane. The membrane was immunoprobed with monoclonal anti-p53 antibody Pab421, polyclonal anti-MDM2 antibody, or monoclonal anti-p21 antibody, respectively, as shown in Fig. 5. Signals were detected by the ECL reagents (Santa Cruz Biotechnology).

RNA or cDNA Probe Labeling. RNA was labeled as described (39). MDM2, p53, and GADPH probes as indicated in Fig. 5 were prepared using the random primer labeling as described (40).

Northern Blot Analysis. Northern blot analysis was carried out as described (40). Total RNA from irradiated or nonirradiated cells was isolated using the Trizol reagent (Life Technologies, Inc.). Fifteen μg of RNA were loaded onto a 1.5% agarose gel and transferred to a nitrocellulose membrane. The membrane was exposed to UV light in a UV cross-linker (Fisher Biotech) and incubated with32P-labeled cDNA probes encoding mouse p53, p21, MDM2, or GADPH at 42°C overnight. After washing with 4× SSC once and 1× SSC [0.15 m NaCl, 15 mM sodium citrate (pH 7.0)] twice, the blot was exposed to X-ray film.

Determination of Cell Growth Rate. Irradiated or nonirradiated cells were treated with trypsin-EDTA solution after washing with PBS at different time points postirradiation. Cells were then counted using a hemocytometer under light microscope. Triple plates were counted for each time point. Data were then plotted in a graph as shown in Fig. 3.

DNA Fragmentation Assays. Irradiation of cells were conducted as described above. Floating or attached cells at different time points after irradiation were harvested separately for DNA isolation, as indicated in Figs. 2 and 4. DNA fragments were detected by using a DNA ladder detection kit purchased from BioSource International, Inc. (Camarillo, CA), as described (41).

T2 RNase Protection Assay. T2 RNase protection assays were performed according to the manual of Ambion, Inc., as described (39).

RESULTS

UV but not γ Irradiation Causes a Massive Apoptosis of F9 or Tera2 Cells. Previously, UV (20 J/m²) and γ-ray (10 Gy) irradiation were shown to cause different patterns of p53 induction (6, 34) in a variety of cells. In γ-irradiated cells, the p53 level displayed a twin peak pattern, peaking at 3 h after irradiation with another low peak after 8 h. However, upon UV irradiation, the p53 level continued to increase even 24 h afterward, if cells survived (40). This obvious difference prompted us to examine whether these two different DNA-damaging sources might lead to distinct phenotypes. Surprisingly to us, when murine teratocarcinoma F9 cells containing wild-type p53 were irradiated with UV or γ-ray, the cells died quickly after being exposed to 20 J/m² UV and almost completely disappeared 24 h afterward, whereas the majority of the cells were still alive after γ irradiation (10 Gy; Fig. 1). The same result was also observed using human testicular carcinoma Tera2 cells (data not shown and Fig. 4). This result is more clearly demonstrated in a growth curve analysis (the middle graph of Fig. 3). The cell death occurred when cells were exposed to either 10 or 20 J/m² UV light. Only 50% of the cells were left at 7 h, and ~95% of them underwent apoptosis within 24 h. Conversely, most of the cells exposed to even a lethal dose of γ-ray (14 Gy) were still alive, and ~90% of the cells were viable 24 h after irradiation, although there was not a significant difference between UV and γ irradiation in the cell viability within the first 5 h (Fig. 3). The massive cell death after UV but not γ irradiation was attributable to an apoptotic mechanism, because DNA fragmentation was detected within 8 h after UV irradiation of F9 cells (Fig. 2). These results clearly indicate that UV and γ irradiation at a median or high dose causes different phenotypes of testicular carcinoma cells.

UV-stimulated Apoptosis of F9 or Tera2 Is p53 Dependent. To test whether UV-induced apoptosis of teratoma cells is dependent

![UV/F9 Cells](image)

Fig. 2. DNA fragmentation in the UV-irradiated F9 cells at different time points. Ten μg of genomic DNA were loaded onto an agarose gel and stained with ethidium bromide. P, attached (plating) cells; F, floating cells.
upon p53, a murine p53 null testicular carcinoma EB-16 cell line was used. This cell line was isolated from the teratoma of p53 knock-out mice (36) and found to be resistant to other apoptosis-stimulating signals (42). As shown in the top panel of Fig. 3, p53 was hardly detectable in this cell line, even when irradiated with 20 J/m² UV light or 10 Gy γ-ray (Lanes 1–3), compared with that of F9 cells (Lanes 4–6). In agreement with studies by others (36, 42), almost all of the EB-16 cells were still alive 24 h after either UV or γ-ray irradiation (Fig. 3, bottom panel). Consistently, DNA fragmentation was not detected after irradiation in either case (Fig. 4). By contrast, DNA fragmentation was found in both p53-containing F9 and Tera2 cells (Fig. 4). Taken together, these results indicate that the massive cell suicide after UV irradiation is dependent upon p53.

Of note in Fig. 4, DNA fragmentation was also detected in γ-irradiated F9 or Tera2 cells, suggesting that γ irradiation induces apoptosis as well (Fig. 3). Then, why were most of the cells still viable after γ irradiation but not UV (Fig. 3)? To address this question, kinetics of p53 induction after irradiation was analyzed in both cases. Again, consistent with previous reports by others and us (6, 34), two distinct patterns of p53 induction at the protein level were observed after UV or γ irradiation (Fig. 5, second panel). The p53 protein level was elevated dramatically upon UV irradiation and continuously increased 12 h after irradiation, whereas after γ irradiation, p53 displayed a twin peak induction at 3- and 12-h points. Also, the level of p53 stimulated by UV irradiation was much greater than that by γ irradiation (Fig. 5, top panel). These differences are well correlated with the different extents of p53-dependent apoptosis caused by the two types of DNA-damaging signals (Figs. 1–4). Thus, the massive apoptosis induced by UV is largely attributable to the remarkably elevated p53 protein in response to this type of DNA damage.

**UV but not γ Irradiation Inhibits MDM2 Expression.** MDM2 has been shown to bind to p53 and mediate its degradation through ubiquitin-dependent proteasome (22, 23). One recent report showed that the expression of MDM2 was inhibited upon UV irradiation (40).

**Fig. 3. Growth curves of F9 or EB-16 cells after irradiation with UV or γ-ray. A, WB analysis of p53 in irradiated F9 or EB-16 cells. One hundred μg of total cell lysates after UV (20 J/m²) or γ irradiation (7 GY) were loaded directly to a 10% SDS gel. Polyclonal anti-p53 antibodies were used for WB. B, growth curves of F9 cells at different time points after irradiation with different doses of UV or γ-ray as indicated. C, growth curves of EB-16 cells at different time points after irradiation with UV and γ-ray as indicated. Bars, SE.**

**Fig. 4. DNA fragmentation in the irradiated F9, EB-16, and Tera2 cells. Ten μg of genomic DNA isolated from cells with or without UV (20 J/m²) or γ-ray (7 Gy) irradiation were loaded onto an agarose gel and analyzed as described above. F and P, floating and attached (or plating) cells, respectively.**

**Fig. 5. UV but not γ irradiation represses MDM2 expression at both the RNA and protein levels. F9 cells irradiated with UV (20 J/m²) or γ-ray (7 Gy) were harvested at different time points after irradiation for WB or Northern blot analyses. One hundred μg of total cell lysates were used for WB analysis of MDM2 (top panel) or p53 (second panel from top) proteins as indicated. Fifteen μg of total RNA were used for Northern blot analysis of MDM2, p53, or GAPDH, as indicated in the three bottom panels.**

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Thus, to check whether MDM2 expression is responsible for a drastic increase of p53 in response to UV irradiation, MDM2 expression was examined, using WB and Northern blot, in cells exposed to UV or γ irradiation. Interestingly, UV and γ irradiation displayed different effects on MDM2 expression. As shown in Fig. 5, both MDM2 protein and mRNA were induced by γ irradiation (10 Gy), peaking at 3 h (Fig. 5, top and middle panels). This MDM2 induction was well correlated with the reduction of p53 5–7 h after irradiation, suggesting that increasing MDM2 may lead to p53 degradation (Fig. 5, second top panel) and thus rescuing most of cells from undergoing apoptosis (Figs. 1 and 3). Conversely, expression of MDM2 at both the protein and RNA levels was remarkably inhibited by UV irradiation (20 J/m²), consistent with the previous report (40). This UV-responsive inhibition appeared to be specific to MDM2, because the expression of p53 and GADPH mRNAs was not affected by the same dose of UV irradiation (Fig. 5, two bottom panels) and other p53 target genes, such as p21, were actually induced by both UV or γ irradiation (Ref. 40; data not shown). Also, the UV-responsive MDM2 repression seemed to be p53 independent, because this inhibition was observed in p53 null cells as well (Ref. 40; data not shown). Taken together, these results indicate that UV but not γ irradiation may turn on a mechanism specifically repressing expression of MDM2, leading to a drastic increase of p53 and subsequently massive apoptosis.

The MDM2 Promoter Harbors a Potential UV-responsive DNA cis Element Negatively Regulating Its Own Expression. The finding that UV irradiation results in transcriptional repression of MDM2 expression suggests that the MDM2 promoter region may mediate this repression in response to UV-caused DNA damage. To test this idea, a set of CAT reporter plasmids driven by a series of truncated MDM2 promoter fragments, as indicated in Fig. 6, was used. These constructs were introduced into murine immortalized fibroblast 12 (1) cells containing wild-type p53 and selected by 0.5 μg/ml neomycin. Each cell line was irradiated with 20 J/m² UV and harvested 6 h after irradiation. RNase protection assays were conducted as described in “Materials and Methods.”

![CAT Reporter: H0.5A-CAT](image)

**Fig. 6.** The UV responsive cis element resides upstream from the p53 binding site within the MDM2 promoter region. RNase protection assays of CAT transcripts under control of different DNA regions of the MDM2 promoter in response to UV irradiation (20 J/m²). Stable cell lines harboring CAT reporter genes, driven by different regions of the MDM2 promoter (as indicated below the top panel), were established by introducing these reporter plasmids, together with vectors residing on a neomycin-resistant gene, into immortalized murine embryonic fibroblast 12 (1) cells containing wild-type p53 and selected by 0.5 μg/ml neomycin. Each cell line was irradiated with 20 J/m² UV and harvested 6 h after irradiation. RNase protection assays were conducted as described in “Materials and Methods.”

In contrast, CAT transcripts increased dramatically after UV irradiation when the CAT gene was driven only by the p53RE-containing region (Lanes 7 and 8). However, this increase did not occur when the longer HincII-XhoI region containing p53RE was used (Lanes 5 and 6), although the PvuII-XhoI region further downstream from the p53-binding site of the promoter did not appear to mediate the UV-stimulated transcriptional repression (Lanes 9 and 10). These results suggest that the MDM2 promoter may mediate a UV-stimulated transcriptional repression through a non-p53RE region.

**DISCUSSION**

Blocking the MDM2-p53 regulatory feedback loop is crucially important for p53 accumulation and activation (26, 28, 30). Here, in this study, we documented a different mechanism that cells use to activate p53 by down-regulating MDM2 transcription in specific response to UV-caused DNA damage. Supporting this conclusion are several lines of evidence:

(a) Upon UV irradiation of F9 or Tera2 cells at 10 or 20 J/m², expression of MDM2 at the protein and RNA levels was completely inhibited within the first 12 h (Fig. 5). Conversely, γ irradiation at 7 or 14 Gy (high dose) resulted in significant induction of MDM2 protein and RNA, peaking at ~3 h. In contrast, this difference, the p53 protein level continuously and dramatically increased after UV irradiation, whereas its induction with a typical twin peak pattern was clearly reduced upon γ irradiation (Fig. 5; Refs. 6 and 34). These results were reproducible using several other mammalian cell lines such as human osteosarcoma U2-OS cells or human astrocytoma SJSA cells, both of which contain wild-type p53 (data not shown).

(b) A region upstream from the p53 binding site within the MDM2 promoter appeared to mediate transcription repression after UV irradiation, (Fig. 6), although a detailed mapping is required for finely defining the DNA repression element in this promoter.

(c) As a consequence, F9 or Tera2 cells underwent massive apoptosis only when the cells were irradiated with UV but not γ-ray (Figs. 1–4). The apoptotic phenotype was largely caused by the dramatically accumulated p53 protein, because apoptosis did not occur when the p53 null EB-16 cells were irradiated with the same dose of UV (Figs. 3 and 4). This massive apoptosis appears to be cell type-specific, because some of the wild-type p53-containing cells, such as SISA or murine fibroblast 12 (1) cells tested in this study, did not display such dramatic cell death (data not shown). Hence, these results demonstrate that UV but not γ radiation suppresses transcription of MDM2 and in turn induces p53, resulting in irreversible and drastic apoptosis of testicular carcinoma cells.

It is puzzling how UV at high doses inhibits MDM2 expression independently of p53 (Fig. 5; Ref. 40), whereas at low doses (<5 J/m²), it induces MDM2 transcription in a p53-dependent manner (40, 44). Decrease of MDM2 expression does not appear to be the result of general transcription suppression by UV, because mRNA synthesis of other genes such as p53, GADPH, or p21 was not inhibited (Fig. 5; data not shown; Ref. 40). Because the UV-responsive MDM2 transcription repression was also observed in p53 null cells (40), it is unlikely that this repression is executed through p53. Then, it is most likely that there may be a cellular UV-activated repressor that can specifically regulate MDM2 RNA synthesis through interaction with a putative UV-responsive, DNA cis element within the MDM2 promoter (Fig. 6). This putative repressor may be turned on only by a high dose of UV irradiation. Identification of the MDM2 transcriptional repressor would ultimately shed light on better understanding of the complicated MDM2-p53 loop regulation.

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4 Unpublished observation.
It is also intriguing why expression of MDM2 needs to be differentially regulated by different doses of UV but not γ irradiation. This must be physiologically significant. γ irradiation at different doses activates the same ATM-chk2 pathway to phosphorylate Ser-20 of p53 and thus to block the binding of MDM2 to p53, leading to p53 induction (8–10). Although it is possible that UV irradiation may trigger a similar pathway to target Ser 20, this type of irradiation certainly uses a distinct mechanism to activate p53 (5, 6). DNA damage caused by a low dose of UV is less detrimental to cells and readily repaired. Upon such irradiation, MDM2 is induced in a p53 dependent fashion to restrict the role of p53 as an apoptosis promoter, allowing cell growth after repair. However, when irradiated with a more deleterious dose of UV, cells are severely harmed and unable to repair the damaged chromosomes. Therefore, these genetically altered cells need p53 to trigger the apoptotic machinery that executes suicide, preventing them from further proliferating. Shuting down the MDM2 expression would be the most efficient way to maintain high levels of p53, thus leading to drastic apoptosis. This may explain why exposure of normal adult human skin to doses of UV irradiation that induced mild sunburn resulted in the dramatic increase of the p53 protein in the epidermis and superficial dermal fibroblasts (45). Interestingly, the p53-induced massive apoptosis of F9 or Tera2 cells attributable to the high levels of p53, thus leading to drastic apoptosis. This may explain how exposure of normal adult human skin to doses of UV irradiation that induced mild sunburn resulted in the dramatic increase of the p53 protein in the epidermis and superficial dermal fibroblasts (45). Interestingly, the p53-induced massive apoptosis of F9 or Tera2 cells attributable to the high levels of p53, thus leading to drastic apoptosis. This may explain the lethality of MDM2 knock-out mice (18, 19).

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