APA F-1 Is a Transcriptional Target of p53 in DNA Damage-induced Apoptosis

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Abstract

The expression of genes involved in p53-mediated apoptosis was studied using cDNA microarray after treating isotopic cell lines with either ionizing radiation or doxorubicin. Most of the known p53 transcriptional activation target genes clustered in a functional category defined by early and p53-dependent induction, regardless of the type of stress. Apoptotic protease activating factor-1 (APA F-1) emerged from this analysis as a novel p53 target gene. Genomic sequences upstream of the APA F-1 transcription start site contain a classic p53-responsive element that binds to p53. Consistently, p53 directly induced APA F-1 gene expression. Furthermore, DNA damage-mediated induction of APA F-1 mRNA and protein expression, accompanied by apoptosis, were strictly dependent on wild-type p53 function. These data are consistent with the hypothesis that APA F-1 is an essential downstream effector of p53-mediated apoptosis.

Introduction

p53 is a central regulator of cellular responses to stress (1). A low level of latent p53 is present in normal cells and is stabilized and activated through posttranscriptional modification, which can lead to cell cycle arrest, DNA repair, or apoptosis. Active p53 functions as a transcriptional transactivator, as well as transrepressor, and participates in a variety of protein-protein interactions (2). Cell cycle arrest mediated by p53 has been clearly correlated with its function as a sequence-specific transcriptional transactivator of genes, such as CDKN1A (p21/WAF-1/CIP1), a cyclin-dependent kinase inhibitor. Transcriptional activation also is thought to play a major role in p53-mediated apoptosis, partly because most p53 mutations are missense in human cancers and map to the DNA binding domain of the protein. p53 mutations can lead to its loss of function as a transcription factor or even a gain in oncogenicity (3). However, despite the fact that active p53 can modulate the transcription of genes involved in apoptosis, defining molecular mechanisms that lead to p53-mediated apoptosis has proven to be complex, and nontranscriptionally mediated pathways also are likely to be involved (2, 4). Recently, certain activating modifications of p53, such as site-specific phosphorylation and acetylation, were found to be dependent on the type of DNA damage (5). Those modifications would then define the genes transcriptionally regulated by p53, and the balance between those downstream targets would lead to transient or permanent cell cycle arrest or apoptosis (6). Through the use of novel technologies, such as serial analysis of gene expression and cDNA microarray hybridization, numerous genes that are transcriptionally regulated by p53 are being identified (7–10). However, in most of these cases, exogenous promoter-driven p53 expression was used to achieve high levels of p53 in immortalized tumor cell lines, without stress-induced modifications or activation. In addition, the end points of such expression (growth arrest, senescence, and/or apoptosis) have not always been considered. If it is true that the type of stress can define a set of inducible genes, then such experimental designs may preclude the uncovering of p53 targets that lead specifically to the induction of apoptosis. Here, through gene expression analysis of isogenic non-tumorigenic cell lines that differ in p53 status and sensitivity to apoptosis, we define a set of genes that participate in a p53-mediated apoptotic pathway. Interestingly, APA F-1 emerged from this screening as a novel p53 target gene.

Materials and Methods

Cell Culture. TK6 and WTK1 are EBV-immortalized human LCLs that have been derived from the same donor. TK6 contains wild-type p53, and WTK1 has a single bp substitution in codon 237 resulting in abnormal p53 protein function (11). Cells were maintained in RPMI medium, supplemented with 15% FBS, p53-null Li-Fraumeni O41-tet fibroblasts (O41-TR) were maintained in DMEM medium, supplemented with 10% FBS, 600 μg/ml Geneticin, 50 μg/ml hygromycin, and 2 μg/ml tetracycline. These fibroblasts are homozygous for a single frameshift mutation at codon 184 of p53 and have been transfected stably with a wild-type p53 CDNA vector under the control of a tetracycline-regulated promoter, allowing for the induction of p53 expression by removal of tetracycline from the growth medium (12). The human colorectal carcinoma cell lines HCT116 and HCT116 p53+/− (targeted deletion of p53; Ref. 13) were maintained in McCoy’s 5A medium, supplemented with 10% FBS. Dox was obtained from Sigma (St. Louis, MO). Irradiation treatments were performed in a Cesium-137 chamber at 4.3 Gy/min. Apoptosis was determined by flow cytometry as described previously (14).

cDNA Microarray Hybridization and Analysis. Cells were lysed with TRizol reagent (Life Technologies, Inc., Gaithersburg, MD), and total RNA was extracted according to the manufacturer’s instructions at 0, 6, and 24 h after treatment with either 0.5 μg/ml Dox or 10 Gy IR. Fluorescently labeled cDNA probes were generated using 40 μg of total RNA by a single round of reverse transcription in the presence of aminolyl-dUTP (Sigma), followed by a coupling reaction to Cy3 or Cy5 monofunctional NHS-ester (Amersham Pharmacia, Piscataway, NJ). Complex probes (usually containing untreated Cy3-labeled cDNA with Dox or IR-treated Cy5-labeled cDNA) were denatured and hybridized to glass slides featuring 6500 cDNA elements (National Cancer Institute Microarray Facility, Advanced Technology Center, Gaithersburg, MD) overnight at 65°C. Slides were washed successively in 1 × SSC/0.1% SDS, 1 × SSC, and 0.2 × SSC for 2 min each, then rinsed in 0.5 × SSC and spin dried. The two fluorescent intensities were measured simultaneously using a GenePix 4000A scanner, and the acquired image was processed with GenePix Pro 3.0 software (Axon Instruments, Union City, CA). The basic raw data and derived ratio measurements were then uploaded to the National Cancer Institute MicroArray Database system, which provides the bioinformatics and analysis tools necessary for the interpretation of gene expression data.

Semiquantitative RT-PCR. Total RNA was extracted using TRizol reagent (TK6, WTK1, and O41-tet cell lines) or RNeasy Mini Kit (HCT116 and HCT116 p53+/− cell lines) from Qiagen, Inc. (Valencia, CA) at the indicated time points after Dox treatment. According to preliminary studies showing a linear range of amplification, 60 ng of RNA were reverse-transcribed and amplified with SUPERSCRIPT One-Step RT-PCR with Platinum Taq (Life Technologies, Inc.) using the following primers: APA F-1 sense 5′-CACGTT-CAAAAGTGGCTGAT-3′, APA F-1 antisense 5′-TGGTCACACTGCAAG-

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2 The abbreviations used are: LCL, lymphoblastoid cell line; FBS, fetal bovine serum; IR, γ-irradiation; RT-PCR, reverse transcription-PCR; PARP, poly(ADP-ribose) polymerase; Dox, doxorubicin.
GACCAT-3', PIG3 sense 5'-CGCTGAAATTCACAAAGTG-3', PIG3 antisense 5'-AACCCATCGACCATCAAGGC-3', β-ACTIN sense 5'-GCTCTGTGTCGACAACCGGCTC-3', and β-ACTIN antisense 5'-CAGATCTGGGTACATCTTC-3'. The following cycle parameters were used: 1 cycle of 50°C for 30 min and 94°C for 2 min (reverse transcription); 25–30 cycles of 94°C for 15 s, 55°C for 30 s, and 72°C for 1 min (PCR amplification); and 1 cycle of 72°C for 10 min (final extension). PCR products were visualized by electrophoresis on 2% Nusieve 3:1 agarose (FMC, Rockland, ME), followed by digital capture using Lumi-imager F1 (Roche, Indianapolis, IN).

Western Blot Analysis. At the indicated time points after Dox treatment, cells were lysed in buffer containing 150 mM NaCl, 0.25% sodium deoxycholate, 1 mM EDTA, 1% Triton-X-100, 0.5% NP40, 1 mM phenylmethylsulfonyl fluoride, 2 μg/ml aprotinin, 1 μg/ml leupeptin, 1 μg/ml pepstatin A, 1 mM Na3VO4, and 20 mM NaF in 50 mM Tris (pH 7.4). Whole cell extracts containing 20 or 30 μg of protein, measured by Bio-Rad protein assay (Bio-Rad Laboratories, Hercules, CA), were separated by 8% SDS-PAGE and electrotransferred onto a nitrocellulose membrane (Bio-Rad). The following primary antibodies were used for protein analysis by standard Western blotting procedures: monoclonal p53 (Ab-6), monoclonal PARP (Ab-2), monoclonal MDM2 (all from Oncogene Research Products, Cambridge, MA), monoclonal primary antibodies were used for protein analysis by standard Western blotting procedures: monoclonal p53 (Ab-6), monoclonal PARP (Ab-2), monoclonal MDM2 (all from Oncogene Research Products, Cambridge, MA), monoclonal APAF-1 (R & D Systems, Minneapolis, MN), and monoclonal anticlone C4 (Boehringer Mannheim, Indianapolis, IN).

Electrophoretic Mobility Shift Assay. Double-stranded synthetic oligonucleotides containing the putative p53-responsive element in the APAF-1 promoter 5'-CACCTCAGACATGCTGAGACCTAGCAGACAAAGCCAGGCGA-3' (upper strand) or bearing a mutation CATG to TCGC in the p53-binding motif (italicized above) were labeled with [32P]ATP using T4 polynucleotide kinase. TK6 nuclear extracts collected after 16 h of Dox treatment were incubated with radiolabeled double-stranded oligomers for 30 min at room temperature in a reaction containing 10 mM HEPES (pH 7.5), 150 mM NaCl, 1 mM MgCl2, 8 mM DTT, 0.03 mM EDTA, and 10% glycerol. Monoclonal p53 antibody PAb421 (Oncogene Science) was added to the reaction mixture to supershift the p53-DNA band. For competition experiments, 2.5 pmol (25-fold excess) of unlabeled double-stranded APAF-1 oligonucleotides or a p53 consensus binding sequence (Santa Cruz Biotechnol- ogy, Santa Cruz, CA) was added to the binding reaction before the addition of the labeled probe. After incubation, each sample was electrophoresed in a native 4% polyacrylamide gel (30:1) using 0.5 × Tris-borate EDTA. The gels were dried and exposed for autoradiography at ~70°C.

Results and Discussion

Identification of p53 Target Genes Involved in Apoptosis. Consistent with previously published results (11, 14), treatment of TK6 LCLs (functional p53) with 10 Gy IR or 0.5 μg/ml Dox resulted in 42 ± 2% and 39 ± 2% apoptosis by 24 h, respectively, but WTK1 LCLs (mutant p53) were completely resistant. Total RNA was extracted at 6 (TK6) and 24 h (TK6 and WTK1) after treatment with either IR or Dox and subjected to cDNA microarray analysis on glass slides featuring 6500 cDNA elements (5831 unique clones) covering 4900 unique genes and expressed sequence tag sequences. RNA extracted from the corresponding untreated cell line was always used as a reference. Complex probes usually contained Cy3-labeled cDNA derived from untreated cells and Cy5-labeled cDNA derived from Dox- or IR-treated cells. All hybridizations were performed in duplicate, with Pearson correlation coefficient >0.8 for all repeat hybridizations. One reverse-fluorescence hybridization (containing Cy5-labeled cDNA derived from untreated TK6 cells and Cy3-labeled cDNA derived from Dox-treated TK6 cells) showed a Pearson correlation coefficient of ~0.86, indicative of a low incidence of color biases, and was included in the analysis as well. Of the 5831 unique clones covered by the cDNA microarray analysis, differential expression >2-fold was seen in ~10% of clones for TK6 cells and ~4% of
clones for WTK1 cells. Fig. 1 shows a graphical view in pseudo-color of gene expression clusters generated by GENE CLUSTER, a hierarchical clustering algorithm that arranges genes and arrays together according to their similarity in patterns of expression (15). In this analysis, genes belonging to a similar functional category tend to cluster together. Hybridization replicates are represented together in the graphical view, demonstrating the reproducibility of our cDNA microarray technique, consistent with a high Pearson correlation coefficient. Interestingly, the overall array similarities among TK6 LCLs, which are not evident in WTK1 cells, were based on the time after treatment rather than the type of DNA-damaging agent. This indicates that p53-mediated responses that lead to the induction of apoptosis may have a similar profile of induction of early and late genes. On the basis of the unsupervised clustering of genes, we were able to define seven clusters or functional categories:

Cluster 1: genes down-regulated early, i.e., 6 h, after DNA damage (e.g., c-myc).

Cluster 2: genes down-regulated late, i.e., 24 h, after DNA damage in a p53-dependent manner (e.g., CDK4, APE/REF-1, CYCLIN A, RRM2, GAS2, and Ku80).

Cluster 3: genes down-regulated after DNA damage independently of p53 (e.g., HSP70).

Cluster 4: genes up-regulated late and in a p53-dependent manner and preferentially after IR (e.g., tumor necrosis factor-related apoptosis-inducing ligand).

Cluster 5: genes up-regulated early and sustained in a p53-dependent manner by both types of DNA damage (e.g., PIG8, PIG3, MDM2, DDB2, CDKN1A, HRAS, BTK2, and APAF-1).

Cluster 6: genes up-regulated late and in a p53-dependent manner and preferentially after Dox (e.g., IRF-7).

Cluster 7: genes up-regulated after DNA damage and independently of p53 (e.g., ATF-3).

To define which p53 transcriptional target genes are involved in the induction of apoptosis by either IR or Dox, we focused on those genes up-regulated early after DNA damage treatment (Cluster 5), because most of the known p53 target genes belonged to this functional category.

Table 1 shows the identity and the average ratio values of gene expression in TK6 LCLs for selected genes with early, p53-dependent induction by 10 Gy IR and 0.5 μg/ml Dox.

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Table 1 Average ratio values of gene expression in TK6 LCLs for selected genes with early, p53-dependent induction by 10 Gy IR and 0.5 μg/ml Dox

**APAF-1** is a novel p53 target in DNA damage-induced Apoptosis. In mitochondria-mediated apoptosis, which occurs in response to DNA damage and other stimuli, mitochondrial depolarization precedes the release of cytochrome c into the cytosol. A complex between APAF-1 and cytochrome c then leads to the recruitment and activation of procaspase-9 to form the apoptosome, the first step in the cascade of caspase activation that ultimately leads to chromatin degradation (16). Because of this pivotal role of APAF-1, it was intriguing that its expression profile placed it along with known p53 transcriptional targets. To determine whether there was a p53-responsive element in the APAF-1 promoter, we referred to the genomic sequence in the bacterial artificial chromosome clone, RP11-45P16 (accession no. AC026112), to which the APAF-1 promoter was mapped previously (17). We found two sites, 13 bp apart (at −604 to −570 relative to the transcriptional start site), that correspond to the consensus palindromic sequence 5′-PuPuPuCa/TT/AGPyPyPy-3′, defined as a p53-responsive element (Ref. 18; Fig. 2A). A radiolabeled APAF-1 wild-type oligonucleotide containing the putative-responsive element (3′-APAF) bound to p53 from Dox-treated nuclear extracts (Fig. 2B). An oligonucleotide with a mutated binding motif (3′-APAF-MT) showed no p53 binding activity. The specificity of this binding was confirmed by showing that oligonucleotides with the wild-type or a consensus binding site, but not the mutant binding site, efficiently competed for the p53/32P-APAF interaction.

To determine whether p53 could directly activate APAF-1 transcription, a p53-inducible cell line (041-TR) bearing a wild-type p53 gene under the control of a tetracycline-responsive promoter was used. Total RNA was analyzed by semiquantitative RT-PCR using specific primers for APAF-1 and β-actin (Fig. 2C). Expression of p53 (as indicated by the p53 immunoblot) resulted in elevated APAF-1 in the absence of DNA damage, indicating that p53 can modulate APAF-1 expression at the transcriptional level.

We next determined whether APAF-1 expression was induced by endogenous p53 activation through DNA damage. In agreement with our original cDNA microarray result, the APAF-1 transcript and protein expression were increased by Dox treatment in TK6 but not WTK1 LCLs (Fig. 3A and data not shown). Resistance of p53-mutant WTK1 LCLs to apoptosis is shown by a lack of caspase-3-mediated PARP cleavage (Fig. 3B). The decrease in APAF-1 expression in TK6 LCLs at 24 h of Dox treatment and concomitant with PARP cleavage is consistent with recent reports indicating that APAF-1 is a target of caspase-3 in mitochondrial and surface receptor-induced apoptosis (Ref. 19 and data not shown). Furthermore, the APAF-1 transcript and protein expression were increased by Dox treatment in HCT116 but not in HCT116 p53−/− colon carcinoma cell lines (Fig. 3, C and D). In both cases, the APAF-1 transcript levels were induced with kinetics similar to that of p53-regulated PIG3 (Fig. 3C and data not shown). APAF-1 protein induction was similar to, although less than, the
used as competitors as indicated above. APAF-1 inhibited by unlabeled oligonucleotides corresponding to the binding site on the C, probes to proteins in nuclear extracts. APAF-1 p53-motif mutant of the binding site on the DNA-p53-PAb421 band is indicated by the mobility shift assay. Anti-p53 antibody PAb421 was present in indicated lanes. Specific APAF-1 and tetracycline. Total RNA was analyzed by semiquantitative RT-PCR using specific primers for absence of DNA damage. p53-null O41-TR fibroblasts were induced to express p53 by above binding sequence is shown putative p53-binding site relative to the transcription start of APAF-1. The consensus p53 gene (targeted p53 deletion), were treated with 1 γ/ml Dox and harvested at the indicated time points for total RNA (C) or protein (D) extraction. C, total RNA was analyzed by semiquantitative RT-PCR using specific primers for APAF-1, PIG3, and β-actin. D, Western blot analysis of APAF-1 protein induction compared with MDM-2 and p53. Actin was used as a loading control. p53-regulated MDM-2 protein (Fig. 3D). Taken together, these results indicate that functional p53 is necessary for DNA damage-induced expression of APAF-1.

APAF-1 and caspase-9 are essential downstream effectors of p53-mediated apoptosis, and their loss promotes oncogenic transformation (20). This association with tumor suppression is strengthened by the fact that melanomas, which rarely show p53 mutations, have a high incidence of APAF-1 loss correlated with resistance to Dox-induced cell death (21). Activated p53 regulates the expression of genes that control mitochondrial membrane permeability and, therefore, the release of cytochrome c during apoptosis (22). It is logical to assume that cytochrome c release is the rate-limiting step in initiating the caspase activation cascade and the main consequence of p53-mediated signals leading to apoptosis. The direct transcriptional activation of APAF-1 adds additional complexity to the network of apoptotic responses activated by p53. In addition, the relevance of our findings is underscored by the fact that overexpression of APAF-1 and caspase-9 restores radiation sensitivity to p53-mutant glioma cells (23).

Our results complement and extend those of Moroni et al. (24) in terms of the ability of p53 to transcriptionally activate APAF-1. The in vitro assays used by both groups to support the identity of p53-responsive elements, namely, reporter activation (24) and electrophoretic mobility shift assay (Fig. 2B), are complimentary. One of the responsive elements found is the same and has a single mismatch from the consensus p53 binding sequence in a nucleotide outside of the contact site. We showed that this site (−604 to −570) is indeed capable of p53 binding. We do not agree with the second responsive element proposed by Moroni et al. (24), because such a site would contain a total of three mismatches from the consensus p53 binding sequence, two of which would be within the contact region. This site has not been tested for direct p53 binding by electrophoretic mobility shift; however, its removal from a reporter construct results in increased p53 responsiveness (24). Therefore, we believe that there is only one p53-responsive element in the APAF-1 promoter. Taken together, our data support the essential role of APAF-1 in p53-mediated apoptosis. Furthermore, we found overall similarities in the profile of genes induced by equitoxic doses of IR and Dox, indicating that the specificity of the genes up-regulated by p53 during the induction of apoptosis may depend on cell type but not necessarily on the type of stress.

![Fig. 2](image1.png)

**Fig. 2.** Identification of the p53-responsive site in the APAF-1 promoter. A, position of the putative p53-binding site relative to the transcription start of APAF-1. The consensus p53 binding sequence is shown above. R, purine; Y, Pyrimidine; W, A or T. B, electrophoretic mobility shift assay. Anti-p53 antibody PAb421 was present in indicated lanes. Specific DNA-p53-PAb421 band is indicated by the arrow. Unlabeled (cold) oligonucleotides were used as competitors as indicated above the lanes. Interaction between DNA and p53 was inhibited by unlabeled oligonucleotides corresponding to the binding site on the APAF-1 gene (A) or a consensus p53-binding sequence within the GADD45 gene (CBS) but not by a p53-motif mutant of the binding site on the APAF-1 gene (MT). *, nonspecific binding of the probes to proteins in nuclear extracts. C, induction of APAF-1 transcription by p53 in the absence of DNA damage. p53-null O41-TR fibroblasts were induced to express p53 by tetracycline. Total RNA was analyzed by semiquantitative RT-PCR using specific primers for APAF-1 and β-actin. A p53 immunoblot [p53 (IB)] confirms the induction of p53.

![Fig. 3](image2.png)

**Fig. 3.** DNA damage-mediated induction of APAF-1 mRNA and protein is dependent on p53. Western blot analysis of APAF-1 induction (A), p53 induction, and PARP cleavage (B) in total cell lysates of TK6 and WTK1 LCLs, treated with 0.5 μg/ml Dox at the indicated time points. Actin was used as a loading control. Numbers below APAF-1 indicate fold-induction respect to untreated. Human colorectal carcinoma cell lines, HCT116 and HCT116 p53−/− (targeted p53 deletion), were treated with 1 μg/ml Dox and harvested at the indicated time points for total RNA (C) or protein (D) extraction. C, total RNA was analyzed by semiquantitative RT-PCR using specific primers for APAF-1, PIG3, and β-actin. D, Western blot analysis of APAF-1 protein induction compared with MDM-2 and p53. Actin was used as a loading control.
Acknowledgments

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References

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