Key Role of a Downstream Specificity Protein 1 Site in Cell Cycle-regulated Transcription of the AP Endonuclease Gene APE1/APEX in NIH3T3 Cells*

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Mutagenesis and cell proliferation are essential steps leading to carcinogenesis. DNA damage and error-prone processing cause mutagenesis (1–3). Endogenous DNA damage frequently includes apurinic/apyrimidinic (AP) sites, of which >10,000/day are estimated to be formed in each mammalian cell (4). Unrepaired AP sites are cytotoxic lesions that block DNA polymerases, but they are also mutagenic, causing base substitution (5). During DNA repair, AP sites are first incised by an AP endonuclease activity (6). The major mammalian AP endonuclease, Ape1, has been characterized at the biochemical and molecular genetic level by several laboratories (7–11). Ape1 protein also harbors weaker 3’-repair diesterase, 3’-phosphatase, 3’-exonuclease, and RNase H activities (12, 13). The 3’-repair diesterase activity is crucial for repair of 3’-phosphoglycolate ends at strand breaks generated by ionizing radiation and other oxidative stress (6, 14).

Ape1 has a second activity as a redox factor (Ref-1) that acts as a reducing donor for oxidized transcription factors such as AP-1 and p53 to restore DNA binding (15, 16). The Ref1 activity depends on a cysteine residue in the Ape1 N-terminal domain unrelated to non-mammalian AP endonucleases of this family; the AP endonuclease activity is located in the conserved C-terminal domain (17, 18). In addition to a second, as yet undefined, role in activating p53 (15), human Ape1 protein has also been implicated in the transcriptional regulation of both the parathyroid hormone (19) and of the APE1 gene itself (20) in response to extracellular calcium.

The embryonic lethality resulting from homozygous deletion of the mouse APE1/APEX gene (21, 22) has limited studies of the in vivo role of the Ape1 protein. Experiments using antisense APE1 RNA are consistent with a role for Ape1 in DNA repair of oxidative and alklylation damage (23, 24). Variations in APE1 expression have been reported. For example, increased levels of APE1 mRNA were found in human cervical cancer tissue (25) and in differentiating cells during wound healing in pig epidermis (26). The mitogenic carcinogen asbestos induced APE1 expression in rat lung cells (27) as did exposure to H2O2 in HeLa (8) or Chinese hamster ovary cells (28). Thus, variations in APE1 expression can occur under different sets of conditions and contribute to cellular resistance to genotoxic damage (8, 24, 28).

Here we investigated the relationship between the cell cycle and APE1 expression in murine fibroblasts and found that transcription peaks in early S phase. Because transcription factors E2F and Sp1 have been implicated as central mediators of transcriptional control during progression into S phase (29), we examined their roles in cell cycle-dependent APE1 expression. We found that E2F had only a minor role; instead, Sp1 appeared to exert the main effect on cell-regulated expression of APE1 via a regulatory site downstream of the transcription start point.

EXPERIMENTAL PROCEDURES

**Cell Culture—**Murine NIH3T3 embryonic fibroblast cells (obtained from ATCC) were grown in Dulbecco’s modified Eagle’s medium supplemented with 10% (v/v) bovine serum (Hyclone) under 5% (v/v) CO2 at 37 °C. For synchronization, cells were plated at 10% confluence in normal growth medium with 10% bovine serum overnight. The cultures were then shifted to starvation medium (0.5% bovine serum) for 48–60 h. To initiate synchronous growth, complete medium containing 10% bovine serum was added.

**Flow Cytometric Analysis—**To monitor the progression of cells through the cell cycle, DNA content was measured by flow cytometric
Cells were rinsed with phosphate-buffered saline, harvested with 0.05% trypsin-EDTA, and pelleted for 7 min at 500 × g. The cells were resuspended in phosphate-buffered saline, recentrifuged, and fixed in 70% (v/v) ice-cold ethanol for >30 min on ice. Immediately before analysis, the cells were pelleted by centrifugation at 500 × g for 7 min and resuspended at 10^6 cells/ml in phosphate-buffered saline containing 50 μg/ml propidium iodide and 1 μg/ml RNase A. The DNA content of the cell samples was measured in a FACSStar Plus cytometer (Beckton Dickinson).

**Northern Blot Assay**—Total RNA extraction was carried out using a commercially available kit (RNasey, Qiagen, Valencia, CA). Samples (15 μg) of total RNA were resolved by electrophoresis in a 1% denaturing agarose gel, transferred to nylon membranes, and hybridized with a 450-bp SmaI-SalI mouse APE1 probe from pBSK-ape1. β-Actin and glyceraldehyde-3-phosphate dehydrogenase cDNA were used as controls. The radioactive signal was measured using phosphorimaging (Bio-Rad GS-525 molecular image analyzer).

**Electrophoretic Mobility Shift Assay (EMSA)**—For supershift assays, competitor DNA were incubated with the protein extract for 10 min before competition experiments, a 10- and 100-fold excess of unlabeled competitor DNA, were added with the probe extract for 10 min before the labeled oligonucleotide probes were added. For supershift assays, polyclonal antibodies (1 μg in 0.5 μl) against Sp1 (Pep2, sc59; from Santa Cruz Biotechnology) or CCAAT box-binding protein (sc61; also from Santa Cruz Biotechnology) were added to the binding buffer for 1 h on ice before addition of the labeled DNA probes.

**RESULTS**

**Cell Cycle-dependent APE1 Expression in NIH3T3 Cells**—The expression of APE1 as a function of the cell cycle was determined in NIH3T3 fibroblasts. As determined using flow cytometry, confluent, nongrowing NIH3T3 cells (see “Experimental Procedures”) were mainly composed of G0/G1 phase cells (85%) and a small proportion of S phase cells (5%). By contrast, exponentially growing NIH3T3 cultures contained a high proportion (45%) of S phase cells. The steady-state levels of APE1 mRNA were monitored by Northern blot analysis and quantified using a phosphorimaging system. As shown in Fig. 1A, APE1 mRNA was 3.6-fold higher in exponentially growing cells than in confluent cells, which suggests that APE1 gene expression is up-regulated during growth. A similar result was obtained with the mouse embryonic fibroblast line 10T1/2 cells (data not shown).

To determine further whether APE1 gene expression is cell cycle-dependent, synchronized NIH3T3 cells were obtained by serum depletion and refeeding. Fig. 1B shows that the cells passed through G1 and entered S phase ~10 h after release from G0. S phase continued for ~8 h, with the proportion of S phase cells peaking at 16 h. The cells entered G2 around 22 h after release from G0. Total RNA was isolated from cells harvested at times corresponding to G0/G1 (0, 5 h), S (10, 14, 16, 18 h), and G0 phases (22 h). Northern blot analysis showed that the level of APE1 mRNA was relatively low in G0/G1 (0 and 5 h) and began to increase as the cells entered S phase (Fig. 1A). The maximal level of APE1 mRNA (5.4-fold increased over G0) occurred at 16 h, and then APE1 mRNA decreased through the rest of S and G2 phases. These results indicate that the expression of the APE1 gene in mouse fibroblasts is cell cycle-dependent, possibly with a specific relation to DNA synthesis and cell proliferation.

**Cell Cycle-associated APE1 Expression Is the Result of Transcriptional Activation but Not Slower RNA Decay Rate**—The observed increase in the steady-state level of APE1 mRNA could be caused by at least two alternative mechanisms, either increased mRNA production by transcriptional activation or decreased mRNA degradation by mRNA stabilization. To address the possibility of transcriptional activation of APE1, we transiently transfected into NIH3T3 cells a construct with the full-length (~1534 to +295 bp) mouse APE1 promoter fused to the LUC reporter gene (31). As shown in Fig. 2, luciferase activity increased gradually, reached a peak at 20 h (5.8-fold relative to 0 h), and then slowly declined. Overall, the luciferase pattern mirrored well the cell cycle-related changes in APE1 mRNA levels, except that the mRNA was ~3–4 h ahead of the luciferase activity. This difference may be the result of the time needed to synthesize luciferase protein. There was no cell cycle variation in the background level of luciferase expressed in cells that had been transfected with a promoterless LUC vector (Fig. 2). Therefore, the cell cycle-dependent changes in

**Mechanism of Cell Cycle-dependent APE1/APEX Transcription**

| Oligonucleotides* | DNA sequence |
|-------------------|--------------|
| Sp1-1w            | CCGGAACCGTGGGCCGAGCCTCGAATCAGTGAACC |
| Sp1-1m            | CCGGAACCGTGGGCCGAGCCTCGAATCAGTGAACC |
| CCAATw            | GGTGCCGAGGGACAACATCATCGCCTGCGCCAGAACACCA |
| CCAATm            | GGTGCCGAGGGACAACATCATCGCCTGCGCCAGAACACCA |
| Sp1-2w            | GTCGATGCTGTCGGGCGGCCAGGGCGAAAGCCG |
| Sp1-2m            | GTCGATGCTGTCGGGCGGCCAGGGCGAAAGCCG |
| E2Fw              | CTCTTGCTAGCGGCTAGATGGCCGAGCCCCCTGTCCTCGTGAAG |
| E2Fm              | CTCTTGCTAGCGGCTAGATGGCCGAGCCCCCTGTCCTCGTGAAG |

* Wild-type sequences are indicated by w, and derivatives with mutated binding sites are designated by m. The mutated sites are underlined.
APE1 gene expression are caused substantially by changes in transcription.

To determine whether changes in the stability of APE1 mRNA might contribute to its variation during the cell cycle, synchronized cells at 0 h and 16 h were treated with the RNA polymerase inhibitor actinomycin D (6 μg/ml), and at various times thereafter, samples were collected to determine the level of APE1 mRNA by Northern blotting. The mRNA degradation rate was not significantly different between G0/G1 phase cells and S phase cells, with a half-life of 1.9 h in both (data not shown). These results suggest that possible changes in mRNA turnover do not account for the variation in APE1 mRNA during the cell cycle. Instead, transcriptional regulation appears to be responsible for most of the cyclic variation in APE1 expression in NIH3T3 cells.

Two Distinct Functional Regions in the APE1 Promoter—To define the promoter region(s) responsible for the growth-regulated expression of APE1, deletion analysis of the promoter was carried out. Nine deletions of the proximal APE1 promoter region were fused to a CAT reporter gene (32). After transient transfection with these constructs, the cells were synchronized, and CAT activity was measured in growing (20 h) and growth-arrested (0 h) cells (Fig. 3). As successive deletions were introduced in the upstream sequence 1534 bp (pCBM14) to 65 bp
(pCBM20) 5’ to the transcription start (32), the S phase APE1 promoter strength remained nearly constant and was always 3–4-fold higher in S phase than in G1 phase cells (Fig. 3). This result was again consistent with the cell cycle-dependent variation in APE1 expression being transcriptional in origin.

Removing an additional 48-bp fragment to generate pCBM18 caused a ~2-fold reduction in APE1 promoter activity in both G1 and S phase cells, although the growth-associated response was still observed (Fig. 3). This observation indicated a loss of basal promoter strength. Four successive deletions from the 3’-side (pCBM10, 16, 7, and 8) from downstream with a fixed upstream end point at -309 bp were also tested. The S phase-dependent expression of APE1 was preserved in pCBM10 (end point at +183), but was lost specifically in pCBM16 (end point at +99), whereas the expression in nongrowing cells was preserved (Fig. 3). This pattern suggested a specific loss of growth-dependent response connected with the deletion of the +99 to +183 region. Further deletion toward (pCBM7) or into the transcription start site (pCBM8) compromised overall APE1 promoter activity (Fig. 3). These experiments provide solid evidence that the upstream region of the APE1 promoter (~65 to -17) functions in basal transcription, whereas the downstream region (+99 to +183) is necessary for the growth-regulated response.

The Downstream Sp1 Site Functions in Growth-dependent Expression of APE1—To identify the important growth-regulated elements located in the two promoter regions, we next tested for functional transcription factor binding sites within these DNA segments. The upstream region (~65 to -17) contains one potential Sp1 binding site and a CCAAT box, whereas the downstream region (+99 to +183) has a second Sp1 site and an E2F consensus site.

To examine the contribution of each element to APE1 promoter activity, a mutation approach was used. Several promoter constructs directing transcription of a LUC reporter gene were engineered by site-directed mutagenesis (for the locations of the mutated sites, see schematic in Fig. 4); the downstream elements were mutated individually in the E2F site to create E2Fm, in the Sp1-2 site to create Sp1-2m, or simultaneously in both to create E2F/Sp1-2m. Similarly, in the upstream region, individually mutated (Sp1-1m) and (CCAAAtm), and double-mutated (Sp1-1/CCAAAtm) promoters constructs were generated. These constructs were transiently transfected into synchronously cycling NIH3T3 cells, and the levels of LUC activity were measured.

The results in Fig. 4 show that the reporters with either of the upstream sites mutated (in Sp1-1m and CCAAAAtm) had reduced overall transcriptional activity in both G1 (0 h) and S phases (20 h) cells compared with the wild-type promoter, but both retained the growth-regulated response. Mutation of the CCAAT site impaired promoter activity somewhat more than mutating the Sp1-1 site, but the double mutation did not amplify this effect (Fig. 4). Thus, both the Sp1-1 and CCAAT sites are important basal promoter elements throughout the cell cycle, but they are not required for the growth-dependent regulation.

Mutation of the downstream Sp1 site in Sp1-2m caused a significant decrease in APE1 promoter activity specifically in S phase cells, but the promoter strength in G1 phase cells was not impaired (Fig. 4). This pattern demonstrated that the Sp1-2 site is critical for the growth-regulated response. In contrast, transcription from the E2Fm construct was comparable with or only slightly less efficient than that of the wild-type promoter (Fig. 4). The activity of the double mutant construct E2F/Sp1-2m was comparable with that of the Sp1-2m construct.

The Regulatory Elements in the APE1 Promoter Show Cell Cycle-regulated Interactions with DNA-binding Factors—We next examined the interactions between DNA-binding factors and the promoter elements identified as described above. We performed EMSA using nuclear extracts from growth-arrested (0 h) and S phase (16 h) NIH3T3 cells. Labeled probes of equal length (39-mer) contained the sites of interest in either the wild-type or the mutated forms. As shown in Fig. 5, incubation of nuclear extracts with labeled probes containing the wild-type Sp1-1 site or the CCAAT box sites generated a DNA protein complex that could be competed by a 100-fold excess of either an unlabeled probe containing the SV40 early promoter Sp1 site (Fig. 5A, lane 4) or an oligonucleotide with the APE1 downstream CCAAT site (Fig. 5B, lane 4), respectively. This result confirmed the specificity of these complexes. This specificity was confirmed further by supershifting with antibodies against Sp1 (Fig. 5A, lane 7) or CCAAT box-binding protein (Fig. 5B, lane 7). Moreover, the Sp1-1 and CCAAT box-binding complexes each were competed by the other cold competitor (Fig. 5A, lane 6, and Fig. 5B, lane 6). Most importantly, both the Sp1-1 and CCAAT complexes were formed in approximately equal amounts with extracts from both growth-arrested and S phase cells (compare lanes 2 and 3 in Fig. 5, A and B). Thus, these complexes do not appear to account for growth-dependent APE1 expression.
The downstream site Sp1-2 formed an abundant complex with S phase cell extracts (Fig. 5C, lane 3), whereas a relatively minor proportion of the probe interacted with factor(s) from growth-arrested cells (Fig. 5C, lane 2). The Sp1-2 binding activity was similar in cycling cells at 14, 16, 18, and 20 h (data not shown). To verify the specificity of this complex, an Sp1-2 mutated probe was used. The mutation eliminated binding of the probe by S phase nuclear proteins (Fig. 5C, lane 9). We also performed Sp1-2 competition experiments using an unlabeled Sp1-1 fragment (specific competitor, s, in Fig. 5C, lanes 4 and 5) or an E2F fragment (nonspecific competitor, n, in Fig. 5C, lanes 6 and 7); only the Sp1-1 oligonucleotide demonstrated significant competition. The nature of the Sp1-2-binding protein was assessed using Sp1-specific antibodies, which produced an EMSA supershift with S phase nuclear extract (labeled ss in Fig. 5C, lane 10). These results demonstrated that transcription factor Sp1 interacts with a downstream site in the APE1 gene in a growth-dependent fashion.

Two protein complexes were detected with S phase cell extracts and a probe containing the APE1 downstream E2F site (Fig. 5D, lane 2). However, these complexes were not affected by either mutation of the E2F site (Fig. 5D, lane 4) or a 100-fold excess of an unlabeled E2F competitor (Fig. 5D, lane 3). The effectiveness of the competitor was demonstrated using an E2F-containing probe from the dihydrofolate reductase gene (E2Fdf) (31) as a positive control (Fig. 5D, lanes 5 and 6). Antibodies against E2F1, 2, 3, 4, and DP1 proteins also failed to generate supershifted complexes with the APE1 E2F probe (data not shown). These data suggest that complexes observed with this probe were nonspecific.

**DISCUSSION**

Unrepaired AP sites in the genome threaten cellular integrity, in that they block replication and are targets for mutagenesis (5, 33, 34). A central mechanism to counteract this threat may be the induction of DNA repair functions, as we have shown here for growth-regulated expression of the APE1 gene. The amount of APE1 mRNA was tightly coordinated with the cell cycle: the message level began increasing at or before the onset of DNA synthesis and continued to rise to a maximum at ~16 h, near the time when DNA synthesis was maximal in our experiments. The increase in the APE1 mRNA level was effective transcriptionally, and the control in response to the cell cycle depended critically on an Sp1 site in the transcribed region of the APE1 gene.

Increased APE1 expression as cells begin DNA replication may help ensure that the DNA template is free of mutagenic and blocking lesions during this critical time. In addition to the thousands of bases lost daily through spontaneous hydrolysis in each mammalian cell (4), oxygen radicals and other metabolic by-products continuously form lesions that enter the base excision pathway through DNA glycosylases (35). Oxygen radicals can also directly form various types of oxidized abasic sites that are substrates for Ape1 (36). It has been suggested that relatively large numbers of unrepaired abasic sites persist in cellular DNA and that these are oxidized forms (37). Whether increased APE1 expression would be especially important for some classes of damage depends in part on whether Ape1 activity is rate-limiting for the repair of those lesions. For example, studies in yeast indicate that AP endonuclease activity is not limiting for BER of alkylated bases (38). In contrast, a recent report shows that Ape1 is limiting for repair of at least one oxidative lesion, the 3’-phosphoglycolate ester (14), and the induction of Ape1 in response to oxidative agents supports increased cellular survival (8, 28). Even when Ape1 itself does not perform the rate-limiting enzymatic step, the protein’s ability to coordinate the binding and activity of other BER enzymes (39–41) may necessitate increased expression during S phase. The proposed function of Ape1 to protect repair intermediates by remaining bound to its incised product (42, 43) could provide another pressure to coordinate its expression with the cell cycle.

Other base excision DNA repair proteins are also up-regulated in coordination with the S phase. This type of expression profile has been known for a number of years for the human uracil-DNA glycosylase (UNG) gene (44). Recently, Bouziane et al. (45) reported a similar transcriptional variation in the expression of the MPG N-alkyl-purine-DNA glycosylase gene in human fibroblasts after serum starvation and refeeding. In their study, which appeared as the experiments we report here were being completed, they also found a cell cycle variation in APE1 mRNA very similar to that we have observed in NIH3T3 cells. Cell cycle-dependent expression of the hMYH glycosylase was also reported recently (46). Coordinated expression of key DNA repair genes with the cell cycle is therefore a general phenomenon that applies to a number of genes and in different organisms, but it is not universal. In one study of Chinese hamster ovary cells, the rates of replicative DNA synthesis (defined as ATP-dependent) and DNA repair synthesis (defined as ATP-independent) were correlated inversely with each other during cell growth (47). Others report that nucleotide excision repair activity (including its coupling to transcription) was similar throughout the cell cycle (48, 49). Thus, the apparent logic of cell cycle-regulated DNA repair expression (removal of mutagenic and replication-blocking damage ahead of replica-
circumstances can mediate the transport of Ape1 to the nucleus (52). APE1 expression has been reported to vary during brain development in mice (53) and to be down-regulated during apoptosis in myeloid leukemia cells (54). It is therefore possible that the role of cell cycle-responsive APE1 expression relates to one of these other functions rather than to DNA repair.

The dependence of cell cycle-regulated expression of APE1 on an internal Sp1 site is a striking feature. Although Sp1 has typically been portrayed as a general transcription factor for TATA-less promoters (55), accumulating evidence indicates that Sp1-dependent transcription is regulated in response to a variety of signals. Upstream Sp1 sites are involved in cell growth and cell cycle regulation of the hamster dihydrofolate reductase (56) and thymidine kinase genes (57) and of the human uracil-DNA glycosylase gene (44). In our work, we found that the upstream Sp1 site (Sp1-1) of APE1 acts in basal gene expression, whereas the downstream Sp1 site (Sp1-2) functions only in response to cell growth.

The distinct roles of the individual Sp1 sites could be the result of their positions or their unique DNA sequence. In our studies, the Sp1-1 DNA sequence competed for nuclear protein binding to Sp1-2 probes (Fig. 5), which suggests that the sequence context of the individual Sp1 sites determines their unique functions. For the Sp1-1 site, this context would include the CCAAT box, which appears to interact via a common protein complex observed throughout the cell cycle (Fig. 5); those data are consistent with previous DNase I footprinting experiments (32). Binding to the Sp1-2 site was strongest in S phase, consistent with the cell cycle role of this site. Phosphorylation of Sp1 has also been implicated in modifying its DNA binding and transcriptional activity (58), including a C-terminal phosphorylation that governs cell cycle-dependent transcription of the mouse dihydrofolate reductase gene (59). Additional experiments will be required to determine the specific contributions of Sp1 phosphorylation and the sequence context of the Sp1-2 site to cell cycle-dependent expression of APE1.

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