p53 Targets Chromatin Structure Alteration to Repress α-Fetoprotein Gene Expression*

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Many of the functions ascribed to p53 tumor suppressor protein are mediated through transcription regulation. We have shown that p53 represses hepatic-specific α-fetoprotein (AFP) gene expression by direct interaction with a composite HNF-3/p53 DNA binding element. Using solid-phase, chromatin-assembled AFP DNA templates and analysis of chromatin structure and transcription in vitro, we find that p53 binds DNA and alters chromatin structure at the AFP core promoter to regulate transcription. Chromatin assembled in the presence of hepatoma extracts is activated for AFP transcription with an open, accessible core promoter structure. Distal (–850) binding of p53 during chromatin assembly, but not post-assembly, reverses transcription activation concomitant with promoter inaccessibility to restriction enzyme digestion. Inhibition of histone deacetylase activity by trichostatin-A (TSA) addition, prior to and during chromatin assembly, activated chromatin transcription in parallel with increased core promoter accessibility. Chromatin immunoprecipitation analyses showed increased H3 and H4 acetylated histones at the core promoter in the presence of TSA, while histone acetylation remained unchanged at the site of distal p53 binding. Our data reveal that p53 targets chromatin structure alteration at the core promoter, independently of effects on histone acetylation, to establish repressed AFP gene expression.

The tumor suppressor protein p53 plays central roles in the regulation of cell growth, cell cycle arrest, and apoptosis. It is activated in response to a variety of DNA damaging agents and has been shown to interact with a number of cellular proteins of both mammalian and viral origins. In general, the functional consequence of p53 DNA binding is transcription activation of target genes with role(s) in cellular stress response, as well as certain developmental pathways (reviewed in Refs. 1–5). More recently, however, examples of p53-mediated transcription repression through sequence-specific DNA binding have been reported (6–9).

We have established that p53 binds within the AFP1 distal developmental repressor region, displacing bound trans-activator HNF-3 (FoxA) protein, and contributes to post-natal, tissue-specific repression of AFP (6). AFP is normally expressed at high levels in the liver of the developing fetus and silenced after birth. Adult expression of AFP is monitored as a tumor marker: aberrant reactivation occurs in up to 85% of all hepatocellular carcinoma cases (reviewed in Ref. 10).

In this study, we find that p53 binds to DNA during chromatin structure organization as an obligate step in transcription repression. DNA binding of p53 mediates distal regulation of AFP transcription through alteration of chromatin structure at the core promoter. The ability of p53 to regulate nucleosome positioning at the core promoter is independent of histone modification. We show that histone hyperacetylation has direct consequences for core promoter chromatin accessibility and gene activation. These effects are overridden by addition of p53, which represses transcription by restricting chromatin accessibility even in the presence of hyperacetylated histone H3 and H4 N-terminal tails at the core promoter.

EXPERIMENTAL PROCEDURES

Plasmids and Solid-phase DNA Templates—AFPlacZ contains 3.8-kilobase pair upstream DNA including proximal and distal promoter and enhancer I, fused to the coding region of β-galactosidase (11). DelA/lacZ is identical except that it contains a 10-base pair deletion in one p53 binding half-site between –850 and –840, as well as a 4-bp mutation in the other half-site. It was constructed by polymerase chain reaction mutation of the previously described AFPmut5 template (6). Solid-phase AFPlacZ and DelA/lacZ templates were coupled to streptavidin-coated paramagnetic beads as described previously (12). The chick adult β-globin plasmid, pUC18SABC/A1, contains the entire promoter, coding sequence, and 3′ enhancer (13).

Protein Expression and Cellular Extracts—Cell extracts were prepared from HeLa and HepG2 (AFP-positive, ATCC catalog number HB-8065) cells as described by Dignam et al. (14) with minor modifications (6). All extracts contained total proteins in concentrations of 5–10 mg/ml. Xenopus egg extract high speed supernatant (HSS) was prepared as described previously (15). Constitutively activated, recombinant p53 protein was expressed from p53Δ30his as detailed previously (16).

Chromatin Assembly and in Vitro Transcription—In vitro chromatin assembly and transcription reactions were performed as reported previously (12). When trichostatin-A (TSA, Sigma) was added to inhibit endogenous histone deacetylases in the Xenopus egg HSS, the 10 mM Me2SO stock solution was diluted to the desired final concentration and incubated with HSS on ice for 10 min prior to bead/DNA addition and

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1 The abbreviations used are: AFP, α-fetoprotein; TSA, trichostatin-A; HSS, high speed supernatant; ChIP, chromatin immunoprecipitation; HAT, histone acetyl transferase; HDAC, histone deacetylase; MAP, multiply antigenic peptide; MNano, micrococcal nuclease; bp, base pair(s); Pu, purine; Py, pyrimidine.
chromatin assembly. For post-chromatin assembly additions, proteins were added after the 1-h chromatin assembly period and incubated for an additional 30 min. Chick β-globin DNA template was added as a control for RNA recovery. Results were quantified by ImageQuant analysis of scanned autoradiograms.

**Restriction Enzyme Accessibility—HincII restriction enzyme accessibility experiments were performed as described previously (17). All restriction enzyme digests were run on a 2% agarose gel and Southern blotted. A 23-bp 32P-end-labeled oligomer corresponding to promoter sequence at +4 to +26, 5’-CCCACTTCCAGCAGTGGCGGG-3’, was used as probe.**

**Acetylated Histones H3 and H4 Antibodies**—The N-terminal 24 amino acids of human N-acetylase modified (4, 9, 14, 18, 20) H3 and (5, 8, 12, 16, 20) H4 were synthesized as the fluorescently labeled N-terminal non-acetylated histone peptide fragment (MAP) by Research Genetics, Inc. (Birmingham, AL). Non-acetyl immunoreactive antibodies were removed by subtracting with a synthetic, N-terminal non-acetylated mixture of H3 or H4 peptides. Finally, antibodies were affinity purified using AcH3 and AcH4 MAP.

Specificity was confirmed by Western blot analysis, under standard conditions, of histones purified by sodium dodecylate treatment and fractionated on acid gel electrophoresis.

**Chromatin Immunoprecipitation—**Chromatin immunoprecipitation (ChIP) assays were performed on *in vitro* chromatin assembled DNA templates. Protein-DNA complexes were cross-linked by exposure to 1% formaldehyde (final concentration) for 10 min at room temperature, followed by 30 min on ice. These reactions were diluted 3-fold in Xenopus egg extract buffer (12) and mixed gently. The supernatant was removed after magnetic concentration, and bead DNA was resuspended in 1× SM2 buffer (500 mM sucrose, 80 mM KCl, 20 mM HEPES, pH 7.5, 3.5 mM ATP, 6 mM CaCl2) plus 1.5 units of micrococcal nuclease (MNase, Roche Molecular Biochemicals) (12). A 5-min incubation with MNase digested cross-linked chromatin into 200–500-nucleotide size fragments, as determined empirically by agarose gel electrophoresis and Southern blotting. After stopping digestion in 20 mM EDTA, 2 mM EGTA (final concentration), 9 volumes of ChIP dilution buffer (16.7 mM Tris-HCl, pH 8.1, 167 mM NaCl, 1% Triton X-100, 0.01% SDS, 1.2 mM EDTA) were added to each sample. This diluted sample of chromatin/protein/DNA fragments was removed as a supernatant from the immobilized paramagnetic beads and divided among several reaction tubes for incubation with control and specific antibodies as described previously (18). The presence of immunoprecipitated DNA sequences was determined by Southern blotting using a slot-blot manifold for binding DNA to GeneScreen Plus membrane (Beckman Chemical Co.). Hybridization with 32P-end-labeled, double-stranded oligomers encompassing AFPI/lacZ sequences from +4 to +26 (promoter probe), from −800 to −830 (p53-binding site), and random-primed labeled full-length template was performed as described previously (17). Results were quantified by ImageQuant analysis of scanned autoradiograms. Values are expressed as a ratio of bound to input, corrected by comparison to no antibody and full-length template controls.

**RESULTS**

**p53 Binding Mediates Transcriptional Repression and Chromatin Structure Alteration**—We employed *in vitro* chromatin assembly of solid-phase AFPI DNA templates to reconstitute repression of AFPI transcription through a distal p53-regulatory element. We showed previously that chromatin assembly by this method establishes physiologically spaced nucleosomes over the entire DNA template and renders *in vitro* transcription tissue-specific, in contrast to nucleosome-free DNA (12, 17). These templates were either transcribed for functional analysis or structurally analyzed for promoter accessibility or histone modification status (Fig. 1A). Nucleosome assembly silences AFPI transcription compared with unassembled DNA templates (Fig. 1B, lane 1, compared with β-globin transcripts). Addition of HepG2 extract, prepared from cultured human hepatoma cells that express AFPI, during chromatin assembly derepresses and/or activates AFPI transcription an average of 5-fold (lane 2). Titration of increasing amounts of recombinant p53, in addition to HepG2 extract, during chromatin assembly represses AFPI chromatin transcription up to 3-fold (lanes 6 and 7). However, p53 introduced after chromatin structure was established had no significant effect on transcription (p53post, average of 1.1-fold increase, lanes 3–5).

We have utilized restriction enzyme accessibility to monitor changes in promoter chromatin structure induced by p53 DNA binding (Fig. 2). HincII restriction digestion at sites that flank the AFPI promoter at −55 and +29, Fig. 2A, correlates with a core promoter region relatively free of a bound nucleosome and open to transcription complex assembly (12, 17). Structural analysis mirrored the functional effects of p53 addition both during and post-chromatin assembly (Fig. 2B). Compared with chromatin assembly in buffer only, HepG2 extract established an open core promoter (lane 3 compared with lane 2). Addition of p53 protein during chromatin assembly revealed a dose-dependent chromatin closure (lanes 4–6, compared with lane 3). The core promoter chromatin structure remained relatively inert to p53 protein addition post-assembly (lanes 7 and 8). A quantitative average of these data and similar experiments are graphed in Fig. 2C. Comparison of both transcription and chromatin structural consequences of p53 addition pre- and post-chromatin assembly support the view that p53 action is primarily at the level of chromatin structure organization rather than targeting modification of an established chromatin structure.

The p53 DNA-binding site within the AFPI upstream region (−860–−830, Fig. 3A) fits the consensus binding sequence for a p53 tetramer at the 5’ half-site (PuPuPuCA/TGPyPyPy) (19). However, this p53 repressor element has a 3’ half-site...
following a 3-base pair nucleotide spacer that deviates from consensus (PyPyPyCTAGPuPyPu). The influence of DNA binding sequence on p53 conformation and function has been described previously (20), but the specific way in which this response element dictates p53 regulation of AFP is not known. Deletion and mutation of the p53-binding site (DelA) abolishes both p53 and HNF-3 binding at this site (data not shown). Consistent with lack of p53 binding, repression of chromatin transcription (Fig. 3B) and structure accessibility at the core promoter (Fig. 3C) are lost.

Histone Modification Does Not Alter p53-mediated Restriction of Promoter Accessibility—Nucleosome positioning, which restricts core promoter access to restriction enzymes and transcription preinitiation complexes, may be affected by histone N-terminal tail interactions with DNA. Chromatin composed of highly acetylated histones, in general, may be more dynamic and readily activated for transcription; whereas, the opposite may be true for underacetylated nucleosomes. Multiple transcription factors interact with protein complexes displaying intrinsic enzymatic activity, such as histone acetyl transferases (HAT’s) or histone deacetylases (HDAC’s), and target modification of chromatin by virtue of their DNA binding ability (recently reviewed in Refs. 21–23). Several studies have shown interactions between both HAT and HDAC complexes and p53, interactions that may promote histone modification, p53 modification, or p53 stabilization (24–30). Our base-line study of histone modification at the core promoter and the p53-binding site revealed no significant variation in histone H3 acetylation between these regions, in the presence or absence of p53. Four separate ChIP experiments were performed and the percent of acetylated histone H3 present at these regions averaged: at the core promoter, 27.8% ± 9.3 (in the absence of p53) and 27.6% ± 9.2 (in the presence of p53); and at the p53-binding site, 35.1% ± 5.7 (−p53) and 32.2% ± 5.9 (+p53).

Although there were no significant variances between histone modification states localized at the core promoter or p53-binding site, there were striking differences in acetylation states when the equilibrium between acetylases and deacetylases was shifted by addition of TSA to Xenopus egg extract in the absence of hepatoma proteins (Fig. 4). In response to in-
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The specific increases in histone H3 and H4 acetylation at the p53 binding site (consensus 5'-half-site (solid line) and non-consensus 3’-half-site (dashed line)) marked above the normal DNA sequence (AFP) and the HNF-3 site below mutated p53 sequence (DelA). DelA lacks the nucleotides indicated by hyphens and has altered bases in lowercase letters. B. p53 binds to DNA to repress transcription. AFP (lanes 1–5) and DelA (lanes 6–9) bead-DNA were transcribed in vitro as chromatin-free (lane 1) and assembled (lanes 2–9) templates. Chromatin was assembled in the presence of buffer (lanes 2 and 6), HepG2 extract (lanes 3–5 and 7–9), plus p53 protein (lanes 4 and 8, 150 ng; lanes 5 and 9, 300 ng), C. p53 binds DNA to alter core promoter accessibility. AFP (lanes 1–5) and DelA templates (lanes 6–10) were incubated in buffer (lanes 5 and 10) or chromatin assembled (lanes 1–4 and 6–9) as described above. HepG2 extract (lanes 2–5 and 7–10) was supplemented with 150 (+, lanes 3 and 8) and 300 (++, lanes 4 and 9) ng of p53 during assembly. Southern blot analysis reveals relative HindIII accessibility of chromatin (84-bp HindIII band).

creasing concentration of TSA, nucleosomes present at the core promoter region increased in both H3 and H4 acetylation 2–3-fold. However, in the local region of p53 binding, histone modification was maintained at a base-line level over the concentration range of TSA (Fig. 4A). Somewhat surprisingly, the presence or absence of p53 protein made little difference to the state of histone modification at all levels of TSA. We find no evidence that p53 alone targets modification of histone tails at the p53-binding site or at the core promoter.

The specific increases in histone H3 and H4 acetylation at the core promoter led directly to derepression of transcription in the absence of any exogenous activator proteins (Fig. 4B). Functionally, the 2–3-fold changes in histone acetylation at the core promoter mediated a 2-fold increase in transcription of chromatin assembled in Xenopus egg extract treated with TSA (lanes 1–5). The increase in transcription was not dependent on the p53/HNF3-binding site, as similar transcription of the DelA AFP template in TSA-treated egg extract also showed transcription increase with increasing TSA (Fig. 4C, lanes 2 and 3 compared with lane 1).

Despite the presence of highly acetylated histones at the core promoter, p53 was able to repress transcription fully when added during chromatin assembly (Fig. 4B, lane 7 compared with lanes 1 and 6). The ability to repress chromatin transcription was absolutely dependent on DNA binding of p53 as the DelA AFP template remained transcriptionally active in the presence of p53 (Fig. 4C, lanes 4 and 5). Restriction accessibility analysis of core promoter chromatin (Fig. 4D) showed a parallel increase of 2-fold in the presence of TSA (lane 3), and repression to base-line levels in the presence of added p53 (lanes 4 and 5), both in parallel with effects on transcription function (Fig. 4B). The ability of p53 to modify nucleosome/DNA interactions at the core promoter, resulting in chromatin structure closure and repression of transcription, is not dependent on tissue-specific factors or targeted modification of histone acetylation and occurs even in the presence of highly acetylated nucleosomes.

DISCUSSION

During hepatic development and post-natal silencing of AFP expression, specific changes in chromatin structure of the AFP gene occur, which likely play a role in regulation (31, 32). Our present study reveals that the functional outcome of p53 DNA binding within the AFP distal repressor region is dictated by chromatin structure organization. Chromatin structure can influence transcription regulation by obstructing transcription factor access to DNA or by facilitating interactions between distal regulatory factors and proximal promoter elements to repress or activate transcription (33–38). Our in vitro chromatin transcription system recapitulates distal regulation of AFP transcription by p53 bound to DNA 850 base pairs 5’ of the transcription start site within the AFP developmental repressor domain. As best studied in Drosophila, distal repressors, like distal enhancers, are essential in regulation of development and differentiation (39).

Proteins that interact with DNA regulatory elements dictate chromatin activation or repression, as well as the consequences of p53 regulation. AFP chromatin is derepressed or activated in the presence of hepatoma extract, but remains transcriptionally repressed when assembled in HeLa extract (17). As shown
here, p53 mediates repression of hepatoma-activated chromatin, but in the presence of HeLa extract a low level of transcription activation is observed instead (40). Thus, the interpretation of p53 protein interaction with DNA, whether activating or repressing chromatin structure, is influenced by multiple trans-acting factors. The timing of these interactions relative to chromatin assembly is important as well. We find that p53 lacks the ability to alter an established, activated chromatin structure. HNF-3 (FoxA) protein, present in the HepG2 extract, mediates core accessibility to HinclI restriction enzyme and basal transcription factors in chromatin transcription (17). Zaret and co-workers (41, 42) established that HNF-3 is an architectural transcription factor that can position nucleosomes along the albumin enhancer, rendering it competent for later trans-activator binding. Thus, HNF-3 acts as primary effector of chromatin modification and derepression, and this established chromatin structure cannot be altered by post-assembly addition of p53. Previous investigations revealed that p53 binding to DNA induces considerable bending and twisting at its binding site, and the inherent sequence-dependent form that DNA assumes greatly affects p53 DNA binding properties (43). The manipulation of DNA and chromatin structure by proteins such as HNF-3 and/or p53 may establish a requisite order of transcription factor binding to induce specific chromatin-repressed or -activated forms. Studies of Swi5p-mediated recruitment of Swi/Snf and SAGA complexes at the yeast HO endonuclease gene promoter (44), as well as temporal recruitment of chromatin remodeling and histone modifying complexes by nu-

**Fig. 4.** p53-mediated repression of AFP transcription occurs even in the presence of hyperacetylated histones at the core promoter. A, addition of TSA promotes hyperacetylation of histones H3 and H4 at the AFP core promoter but not at the p53-binding site. ChIP analyses of H3 (white bars) and H4 (shaded bars) acetylated histone populations present at the core promoter region (open bars) and the p53 binding region (hatched bars) were performed on in vitro chromatin-assembled AFP templates in the presence (+, 300 ng) or absence (−) of p53. Chromatin was assembled in Xenopus egg extract, incubated in increasing amounts of TSA: none, 10 nM, 100 nM, and 3 μM. Histone acetylation levels were expressed as a ratio compared with base-line values determined in the absence of TSA (see “Results”). These TSA titration experiments were performed twice, thus S.D. values are not presented. B, histone hyperacetylation leads directly to derepressed chromatin transcription that is silenced by p53 addition. Xenopus egg extract incubated in the presence of 0, 10 nM, 100 nM, 3 μM, and 10 μM TSA was used to assemble bead-DNA into chromatin and transcribed (lanes 1–5, respectively). p53 (300 ng) was added during chromatin assembly (lanes 6 and 7) in egg extract incubated in the presence of 0 (lane 6) or 3 μM TSA (lane 7). RNA recovery control primer extension analysis of added β-globin DNA template was performed separately on these reactions (small gel inset). C, p53-mediated silencing of TSA-derepressed transcription requires DNA binding. DelA bead-DNA was assembled in chromatin as described above, using Xenopus egg extract incubated in the presence of 0 (lane 1), 3 μM (lanes 2, 4, and 5), and 10 μM (lane 3). p53 protein was added during chromatin assembly (lane 4, 150 ng; and lane 5, 300 ng). D, p53 mediates core promoter closure even in the presence of hyperacetylated histones. HinclI restriction accessibility was performed on AFP templates in the absence of chromatin assembly (lane 1) or when assembled into chromatin (lanes 2–5). Chromatin was assembled in Xenopus egg extract incubated in no TSA (lane 2) or 10 μM TSA (lanes 3–5). Addition of p53 (+, 150 ng, lane 4; ++, 300 ng, lane 5) altered chromatin accessibility to HinclI enzyme.
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clear receptors (45), support the idea that only specific transcription factors can interact with chromatin to initiate a series of regulatory steps. This temporal order is likely influenced by flanking DNA sequence, the complexity of the regulatory element(s), and interacting proteins.

Our results showing that p53 cannot bind and repress a previously activated chromatin template are in contrast to p53 action at a chromatin-repressed (assembled in buffer) p21 gene template (46). In this case, p53 can bind to chromatin and target p300 to acetylate histone tails at a p53-binding site, which then spreads distally to the core promoter. Together, p53 and p300 activate transcription of chromatin-repressed p21 gene templates. The ability of p53 protein to target histone modification was also suggested by previous studies. Transcription repression of the MAP4 gene is correlated with p53-mediated histone deacetylation and promoter-localized histone modification in cultured cells (24). Our studies of histone modification revealed little change in histone acetylation mediated by p53 addition during chromatin assembly in untreated Xenopus egg extract. When the equilibrium between histone acetylation and deacetylation activities was shifted toward acetylation by TSA addition, the p53-binding site region was maintained in egg extract. When the equilibrium between histone acetylation and promoter-localized histone acetylation/deacetylation equilibria may be revealed by disruption of histone acetylation or deacetylation activities (47), which exist endogenously in Regional, regulated shifts in acetylation/deacetylation equilibria may be revealing a hierarchy of transcription regulation by p53 in which distal alterations in chromatin structure rather than local modification of histone tails play a key role in repressing AFP gene expression. It will be of great interest to compare other p53-repressed and -activated genes and establish whether the interpretation of p53 induction as a transcription activation or repression signal is dictated by DNA regulatory site complexity, interacting proteins, and consequent chromatin structure alteration.

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