Transcription Factor FoxA (HNF3) on a Nucleosome at an Enhancer Complex in Liver Chromatin*

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Nucleosome-like particles and acetylated histones occur near active promoters and enhancers, and certain transcription factors can recognize their target sites on the surface of a nucleosome in vitro; yet it has been unclear whether transcription factors can occupy target sites on nucleosomes in native chromatin. We developed a method for sequential chromatin immunoprecipitation of distinct nuclear proteins that are simultaneously cross-linked to nucleosome-sized genomic DNA segments. We find that core histone H2A co-occupies, along with the FoxA (hepatocyte nuclear factor-3) transcription factor, DNA for the albumin transcriptional enhancer in native liver chromatin, where the enhancer is active. Because histone H2A on nuclear DNA is only known to exist in nucleosomes, we conclude that transcription factors can form a stable complex on nucleosomes at an active enhancer element in vivo.

The crystal structure of the nucleosome core particle reveals how the four core histone proteins within the histone octamer alter DNA structure and accessibility (1). Specifically, the DNA is bent and in some places kinked on the nucleosome (2, 3); histone binding occludes part of the DNA surface; and the nearly two wraps of DNA around the histone octamer place the double helices in close proximity. Although much research has focused on the ways these parameters are inhibitory to transcription factor binding, DNA bending and interactions with histones could promote certain factors to bind nucleosomes, and DNA wrapping can bring cooperative sites together. Furthermore, targeting of chromatin-modifying complexes and other gene regulatory proteins (4, 5) to inactive, closed chromatin domains would appear to require prior specific DNA binding by factors that are not inhibited by nucleosome structure. We recently found that the FoxA (HNF3)† transcription factor, one of the first factors to bind the albumin gene in development (6), can bind its sites on nucleosomal DNA in vitro, regardless of histone acetylation state (7). However, whether factors such as FoxA can bind to nucleosomes in vivo is not clear and is the subject of this paper.

If initial DNA binding factors are not inhibited by nucleosomes, might such factor-bound nucleosomes persist as parts of active gene regulatory complexes? Consistent with this idea, a variety of transcriptional enhancers have been found to exist in a short array of nucleosome-like particles in the cell types in which the enhancers are active (8–13), including the albumin gene enhancer (14). Also, there are now many examples of chromatin immunoprecipitation data indicating that acetylated core histone proteins are in the vicinity of regulatory sequences to which transcription factors are bound. Furthermore, genome-wide studies in yeast showed that depletion of core histone proteins causes a decrease in expression of a significant fraction of genes (15), indicating that histones could contribute positively to their expression.

In all such instances in which nucleosomes are not inhibitory to factor binding in vitro, in which nucleosomes may be positive for enhancer function, or in which histones are in the vicinity of chromatin-bound factors, it has not been determined whether transcription factors can stably co-occupy their target sites with core histone proteins in the native chromatin of a cell. Specifically, the existing models are drawn from nuclease cleavage patterns that resemble nucleosome ladders but that might reflect “enhanceosome” complexes consisting solely of transcription factors bound to DNA (16, 17). A significant prior study revealed a depletion of linker histone H1 but not of core histone H2B, during glucocorticoid receptor binding to mouse mammary tumor virus nucleosomes in cells (18). However, these and other chromatin immunoprecipitation data could reflect transcription factors and histones being bound to DNA in separate subpopulations of cells. In this paper, we asked whether, in native chromatin, transcription factors and core histone proteins could be bound simultaneously to the same underlying DNA segment.

Our approach has been to perform sequential immunoprecipitations of proteins bound to the serum albumin gene enhancer in the native chromatin of liver cells, focusing on the FoxA (HNF3) transcription factor. In vivo footprinting studies have shown that in mouse liver, where virtually all hepatocytes express the albumin gene, FoxA binding sites that are essential for enhancer activity are occupied by protein (6, 14). The extent of footprint protection indicates that the FoxA sites are occupied in the majority of hepatocytes that populate the liver. The N1 nucleosome-like particles at the albumin enhancer, observed by micrococcal nuclelease digestion of liver nuclei, is positioned over the FoxA binding sites and is DNase I-hypersensitive. In contrast, in nonliver tissues, where the FoxA sites are not occupied, nucleosome-like particles are not precisely positioned over the enhancer, and the enhancer is not hypersensitive (14). Although the albumin enhancer and the albumin promoter are separated by 10 kb, these elements are simultaneously DNase I-hypersensitive on individual albumin genes in liver nuclei, suggesting that most of the factor-bound enhanc-

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† The abbreviations used are: HFN, hepatocyte nuclear factor; PCR, polymerase chain reaction; bp, base pair.
ers are active (19). In addition, purified FoxA protein in vitro binds to its sites on nucleosomes with a lower off rate than on free DNA (7). Herein, we used several approaches to show that the high percentage of occupancy of FoxA factors on active, nucleosome-like enhancer complexes in liver nuclei reflects co-occupancy with core histone proteins. The results indicate that nucleosomes can serve as positive architectural components of gene regulatory complexes.

**EXPERIMENTAL PROCEDURES**

**Analysis of Solubilized Liver Nucleosomes—**Liver nuclei were isolated essentially as described by Kornberg et al. (20). Nuclear pellets were resuspended in Kornberg buffer C, warmed to 37 °C for 60 s, and then digested with added MNase for an additional 60 s. Reactions were adjusted to 25 mM EDTA and placed on ice. Aliquots of chromatin were removed for analysis of bulk digestion and indirect end label analysis by Southern blotting (19). The remaining chromatin was gently rocked at 4 °C for 5 min and spun at 15,600 × g for 5 min, and the supernatant containing solubilized nucleosomes was removed and saved. To isolate DNA, aliquots of bulk and solubilized chromatin were incubated in 10 mM Tris-Cl, pH 7.4, 0.1 mM NaCl, 1 mM EDTA, 1% SDS, and 0.1 mg/ml proteinase K at 57 °C for 15–24 h, extracted once with phenol-chloroform and twice with chloroform alone, ethanol-precipitated, and resuspended in 10 mM Tris, pH 7.5, and 1 mM EDTA. For Southern blot analysis of solubilized nucleosomes, 1.6 µg of DNA/lane was electrophoresed on a 1.6% agarose gel, transferred to Duralon membranes (Stratagene), and UV cross-linked. Dot blots with 1–100 pg of albumin enhancer-containing plasmid on a separate membrane were included in the hybridizations as an internal control to measure the efficiency of hybridization of the different oligonucleotides. Oligonucleotide probes corresponded to the N1 particle at the cHNF3 site (oligo B), the upstream linker region (oligo A), and the downstream linker region (oligo C), where the linker and N1 particle regions were defined by the LM-PCR analysis of McPherson et al. (14). Blots were analyzed with a Fuji BAS phosphor imager and autoradiography.

**Chromatin Cross-linking—**C3H male mice were killed by vertebral dislocation, and their abdominal cavities were opened. The livers were removed, placed on ice, and sonicated with a Branson 250 sonifier mounted with a microtip for two 30-s pulses (duty cycle constant; output, 20%). Cross-linking was reversed by incubating at 68 °C for 5 min and then adding 100 mM Tris-EDTA for PCR analysis. The digested DNA, aliquots of bulk and solubilized chromatin were incubated in 10 mM Tris-Cl, pH 7.6, 60 mM KCl, 15 mM NaCl, 0.2 mM EDTA, pH 8.0, 0.5 mM EGTA, pH 8.0, 0.34 µM sucrose, 0.15 mM 2-mercaptoethanol, and 125 mM glycine) and hybridized overnight at 4 °C. The remaining chromatin was digested with proteinase K, extracted with phenol-chloroform, and ethanol-precipitated in the presence of 10 µg of glycogen as carrier. The final immunoprecipitated DNA products were resuspended in 30 µl of Tris-EDTA for PCR analysis.

**PCR Analysis of Immunoprecipitated DNA—**Each PCR amplification was performed using 75% of the immunoprecipitated DNA products in a final volume of 50 µl. PCR reactions contained a 2 ng/ml concentration of each primer, 1 ng of 32P end-labeled primer, a 0.25 ng/µl concentration of each dNTP, 3 mM MgCl₂, 4% Me₂SO, 1× PCR buffer (Perkin-Elmer), and 2.5 units of Taq DNA polymerase. PCR conditions for all primers were initial denaturation at 94 °C for 4 min; 26, 29, and 32 cycles of 94 °C for 30 s, 60 °C for 90 s, and 72 °C for 45 s; and final elongation at 72 °C for 5 min. Amplification products were analyzed on 1.6% agarose gels, which were deburred, dried, and exposed on Kodak XAR film. Signals were quantitated with a Fuji BAS phosphor imager. PCR reactions used the following primers: N1 particle (161 bp), 206 (5'-CGAGATGTTCTTGGTCTTCCTCG-3') and 276 (5'-GGACAGGAGGTTATTGTTAGCG-3'); and N2 particle (66 bp), 596 (5'-TCTGCAACGACACCGAGAGCA-3') and 597 (5'-GGCTGGTGGAGGACGAAATAGGA-3').

**Southern Blot Analysis of Cross-linked Chromatin Fragments—**Partially sonicated, cross-link-reversed genomic DNA (25 µg) was digested with MnlI and electrophoresed on a 1.5% agarose gel. The gel was depurinated for 10 min in 0.25 M HCl, denatured for 20 min in 1.5 M NaCl and 0.5 M NaOH, and neutralized for 10 min in 1.5 M NaCl and 0.5 M Tris, pH 7. Samples were transferred onto a nylon membrane (Du- ralon-UV; Stratagene) with 20 × SSC (3 M NaCl and 0.1 M sodium citrate, pH 7) by capillary transfer and UV cross-linked with a Stratallinker (Stratagene). The blot was prehybridized for 4 h at 65 °C in 10 ml of hybridization buffer (5 × SSC, 5 × Denhardt’s solution, 1% SDS, and 0.1 µg/ml denatured sonicated salmon sperm) and hybridized overnight at 65 °C in 5 ml of hybridization buffer containing 5 × 10⁶ cpm of N1 sequence probe. Blots were internally labeled with α-32P-PCR bands excised above and below the N1 sequence probe. The blot was washed with 0.2 × SSC and 0.1% SDS twice for 15 min at 65 °C and exposed to Kodak XAR film for 10 days with intensifying screens.

**In Vitro Transcription, Translation, and HNF3 Immunoprecipitation—**Mouse Foxa1 (HNF3α) full-length protein was generated by in vitro transcription from plasmid pET28b-mHNF3α (28) followed by in vitro translation with 35S, using rabbit reticulocyte lysates (27).

**RESULTS AND DISCUSSION**

**Albumin Enhancer Sequences Co-fractionate with Nucleosomes from Liver Nuclei—**We first sought to determine whether in liver nuclei, the N1 particles positioned at the upstream linker of the enhancer share biochemical solubility properties of nucleosomes. Southern blotting was used to assess the nucleosomal phasing pattern over the albumin enhancer in liver chromatin digested with a low concentration of MNase. Under conditions in which ~50% of the albumin genes in the nuclear population remain undigested, an indirect end label probe shows that MNase discretely cleaves the boundaries of the ~180-bp N1 region of the enhancer sequence (N1; Fig. 1A, lane 2). The N1 sequence spans Foxa binding sites for the albumin enhancer (Fig. 1D). We next determined whether much higher concentrations of MNase would release the N1 particle and solubilize it as a mononucleosome. Liver nuclei were digested so that the majority of chromatin was in fragments of one to seven nucleosomes in length (Fig. 1B, lanes 3–5). The digested liver nuclei were pelleted, and the solubilized material in the supernatant was analyzed. Under these conditions, the super-
Fig. 1. Nucleosomal conformation of albumin enhancer N1 sequences in liver nuclei. A, indirect end label analysis of EcoRI-digested DNA from liver nuclei treated (+) or not (−) with MNase. Arrows indicate MNase cleavages at discrete positions along the albumin enhancer. B, agarose gel analysis of DNA from liver nuclei that were digested extensively with MNase (lanes 2–5) and of DNA from particles solubilized by the MNase treatment (lanes 6–9). C, SDS-polyacrylamide gel electrophoresis analysis of proteins released from particles solubilized by the MNase treatment (lanes 6–9). D, oligonucleotide hybridization probes: N1, N2, and Foxa (HNF3). E, Oligonucleotide hybridization to Southern blots of DNA from solubilized nucleosomes as seen in B.

Three sets of DNA from solubilized nucleosomes were run on an agarose gel (Fig. 1E, bottom panel) and blotted to a nylon filter. The filter was cut into three strips, and each was hybridized to an oligonucleotide probe for either the middle of the N1 region (Fig. 1D, probe B) or the expected linker regions flanking N1 (Fig. 1D, probes A and C). As seen in Fig. 1E, top panel, sequences hybridizing to the N1 probe B exhibited strong enrichment in the nucleosome fraction, whereas sequences hybridizing to probes A and C were under-represented. As described under “Experimental Procedures,” we controlled for probe hybridization efficiency. We conclude that albumin enhancer sequences spanning the N1 region are in a nucleosome-like conformation in liver chromatin.

Isolation of Specific Nucleosome Cores from Native Chromatin: Cross-linking—To avoid potential artifacts of chromatin rearrangement that might occur during the isolation of nuclei (28), we performed chromatin cross-linking in intact liver cells. Although it is convenient to isolate hepatocytes by collagenase perfusion of intact livers or to study liver cell lines, hepatocyte dedifferentiation commences shortly after disruption of the three-dimensional organization of the liver, as seen by the rapid decline in the transcription rates of liver-specific genes (29). We therefore established conditions for perfusing mouse livers in situ with 1% formaldehyde, thereby cross-linking hepatocyte chromatin in the native tissue environment (see “Experimental Procedures”).

Unlike the results with the non-cross-linked chromatin described above, Southern blotting of the cross-linked chromatin revealed that even high levels of MNase only partially digested the albumin enhancer N1 sequence to mononucleosome-sized particles (data not shown). Under such conditions, MNase digestion of bulk cross-linked chromatin was partially inhibited, although the majority of DNA was still in mono- and dinucleosome-sized fragments. Apparently, cross-linking generates structures at a number of genomic sites, including the albumin enhancer, that are refractory to MNase digestion.

To assess whether core histones are bound specifically to the albumin enhancer N1 region by immunoprecipitation, it was critical to digest the cross-linked chromatin at the boundaries of the N1 region seen in liver nuclei. If the chromatin was sonicated extensively to nucleosome-sized fragments, the fragments would still represent a mixed population with regard to their content of enhancer N1 sequences versus adjacent sequences, and we wished to establish definitively whether the N1 sequence was nucleosomal. We therefore developed a procedure (Fig. 2A) in which the perfusion-cross-linked chromatin was first sonicated partially, purified on CsCl gradients (Fig. 2C), and the soluble fractions were pooled, treated with RNase, and dialyzed. The relatively large purified chromatin segments were then digested with the restriction enzymes MnlI. Extensive trial experiments showed that quantitative MnlI digestion was facilitated by the partial sonication, gradient purification, and RNase treatment. MnlI cuts in the linker regions on either side of the albumin enhancer N1 particle, yielding an N1 fragment of 198 bp; MnlI also releases an 85-bp fragment within the N2 particle (see Fig. 2B). When MnlI was used to digest...
chromatin from perfusion cross-linking experiments, and the DNA was then thermal-reversed and analyzed by Southern blotting, it quantitatively revealed the N1 sequence within the correctly sized MnlI fragment (Fig. 2D, lane 2). Similar analysis with an N2 region probe detected the expected MnlI fragment, although it was much fainter (data not shown), perhaps because cleavage of these sites is inhibited on the N2 particle (Fig. 2B). In conclusion, MnlI can access the linker regions that flank the N1 particle in cross-linked chromatin, whereas MNase cannot. Thus, proteins that would co-immunoprecipitate with the N1 MnlI DNA fragment would be bound specifically to this sequence.

Isolation of Specific Nucleosome Cores from Native Chromatin: Immunoprecipitation—Chromatin immunoprecipitation experiments that use parallel immunoprecipitation reactions for distinct proteins cannot distinguish whether the proteins are bound to the same DNA molecule or whether they are bound to two distinct DNA molecules, of the same sequence, in the population. To address whether individual albumin N1 MnlI fragments are simultaneously bound to HNF3 and core histone proteins, we developed a sequential, rather than parallel, chromatin immunoprecipitation procedure. We first bound HNF3 antisera (24) and preimmune control serum covalently to protein A-Sepharose beads. Covalent binding of antibody to beads would prevent antibody from the first immunoprecipitation, after release of antigen, from persisting through a second immunoprecipitation. We sought to first immunoprecipitate HNF3, rather than the core histones, because the latter were in vast excess in the input chromatin. 35S-labeled, in vitro-translated HNF3 was efficiently immunoprecipitated by the HNF3 antibody beads but not by the preimmune beads (Fig. 3A, compare lanes 2 and 6). To establish sequential immunoprecipitation conditions, we tested a brief exposure of acid or base to elute 35S-labeled HNF3 from the beads (30). Base but not acid treatment efficiently eluted immunoprecipitated HNF3 from the HNF3 antibody beads (Fig. 3A, lanes 7 and 8). We then used the antibody beads for immunoprecipitation with perfusion-cross-linked, MnlI-digested liver chromatin. After immunoprecipitation, the pulled-down chromatin material was subjected to thermal reversion of the cross-links, DNA purification, and PCR cycle step analysis with primers specific to the N1 and N2 enhancer MnlI fragments (Fig. 2B). We used PCR increments of three cycles to the level at which background preimmune and no-antibody control signals were just above detection levels (Fig. 3B) and then quantitated the HNF3 immune signal to preimmune control ratios (Fig. 3C). In most experiments, the preimmune and no-antibody signals were within a few fold of each other. Phosphorimager analysis showed that, within the exponential range of two independent chromatin immunoprecipitation and PCR experiments, the N1 region was enriched an average of 10-fold by the HNF3 antibody beads, relative to the preimmune beads, whereas the N2 region was enriched ~0.5-fold by the HNF3 antiserum relative to the control (Fig. 3C). Note that the N2 region lacks an HNF3 binding site (31). Thus, the N1 region was selectively immunoprecipitated compared with the N2 region.

These data corroborate prior in vitro footprinting and trans-activation data (6, 14, 24, 32) by showing that HNF3 protein indeed occupies the albumin enhancer N1 region. The data also show that proteins binding to the N1 region can be distinguished from those binding to immediately flanking sequences in chromatin.

Albumin Enhancer Complexes Containing HNF3 and Core Histone Protein—We first screened previously characterized antibodies to histone H2A, H2B, and H3 (25, 33) and commercial antibodies to the N-terminal 20 amino acids of histone H3 and acetylated H3 (Upstate Biotechnology) for their ability to immunoprecipitate albumin enhancer sequences. The H2A and commercial H3 antibodies markedly immunoprecipitated the enhancer N1 sequence relative to controls (Fig. 4, A, lanes 11 and 12, and B, lanes 10 and 11). The acetylated H3, noncommercial H3, and H2B antibodies also enriched the N1 sequence but not as strongly (Fig. 4, A, lanes 6, 9, and 15, and B, lane 15). Limited experiments with the antibodies immunoprecipitating purified core histone proteins showed that the most effective antibodies were also more effective in the chromatin immunoprecipitation experiments (data not shown). In summary, most of the core histone proteins are detectable at the albumin enhancer N1 sequence.

To determine whether HNF3 co-occupies the albumin enhancer with core histone proteins, we performed sequential immunoprecipitations with HNF3 antibody beads and then antibodies to core histone proteins H2A and H3, which were strongly positive in single immunoprecipitations. Liver chromatin was cross-linked by perfusion, partially sonicated, purified, digested with MnlI, immunoprecipitated with anti-HNF3 antibody beads, released and rapidly brought to neutral pH, and then immunoprecipitated with a subset of the original panel of anti-core histone antibodies. PCR cycle step analysis of the final products showed that the anti-H2A antibody robustly immunoprecipitated the albumin enhancer N1 sequence relative to the control antibody for the H2A reaction (Fig. 5A, lanes 4–9). Importantly, the low signals in the control antibody reaction demonstrate that HNF3 antibody was not released from the beads during antigen elution. These data show that histone H2A is part of a nucleoprotein enhancer complex containing the transcription factor HNF3. Notably, in all known instances of H2A bound to DNA in nuclei, the histone is within a nucleosome core particle (34).

Neither of the histone H3 antibodies that worked in single immunoprecipitations was able to immunoprecipitate the N1
We expect that histone H3 should be in such an enhancer nucleosome complex, although it was not detected by sequential immunoprecipitation. We suggest that bound HNF3 or other enhancer binding factors hide the histone H3 epitope in the enhancer complex. This is underscored by recent evidence that HNF3 protein interacts directly with histone H3 and not H2A, and that NF1, another factor present at the N1 enhancer complex (14), also binds to core histone H3 (35). Thus, at least two albumin enhancer binding factors could mask an H3 epitope on a nucleosome.

In conclusion, we suggest that core histone proteins can serve as an architectural component that could promote specific transcription factor interactions within a stable, higher-order enhancer complex. The co-occupancy of nucleic DNA by HNF3 and H2A and many recent studies that have found transcription factors and core histones that are separately immunoprecipitable at other enhancers and promoters suggest that nucleosomes might be intrinsically positive in many contexts of eukaryotic gene regulation.

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