Activation of Apolipoprotein AI Gene Transcription by the Liver-enriched Factor HNF-3*

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Liver-specific expression of the apolipoprotein AI (apoA-I) gene is controlled by the coordinate action of transcription factors bound to three sites (A, B, and C) located within a powerful liver-specific enhancer which spans the -222 to -110 region upstream of the apoA-I gene transcription start site (+1). Sites A and C bind various members of the nuclear receptor superfamily including the liver-enriched factor HNF-4. In the current report, enhancer derivatives with mutagenized protein-binding sites were tested for their ability to stimulate the apoA-I basal promoter in hepatoblastoma HepG2 cells. The results revealed that occupation of both sites A and B, but not C is essential for high level expression. Electrophoretic mobility shift assays showed that in HepG2 cells site B is occupied by the liver-enriched factor HNF-3β. Binding of HNF-3β to site B transactivates the apoA-I basal promoter in hepatic and nonhepatic cells. HNF-3β binding and transactivation were dependent upon the close proximity of two HNF-3β binding motifs within site B. Furthermore, HNF-3β and HNF-4, bound to their cognate sites within the apoA-I enhancer exhibited strong synergy in transactivation of the apoA-I basal promoter in nonhepatic cells, highlighting the central role of HNF-3β in liver-specific transcription of the apoA-I gene. It is concluded that cooperative binding of HNF-3β to site B and synergistic interactions between HNF-3β and HNF-4 bound to their cognate sites in the apoA-I enhancer may play a fundamental role in apoA-I gene expression in liver.

Tissue-specific and developmental expression of eukaryotic genes involves the coordinated formation of nucleoprotein complexes comprising the basal and upstream transcriptional machinery (reviewed in Ref. 1). Liver-specific expression is regulated by multiprotein complexes which contain both liver-enriched and ubiquitous transcription factors (reviewed in Ref. 2). Synergistic interactions between the proteins in these complexes influence the establishment, maintenance, and regulation of hepatocyte-specific transcription.

The expression of apoA-I, a major component of high density lipoprotein (reviewed in Ref. 3), is restricted primarily to the liver and small intestine (4-7). The -222 to -110 region of the apoA-I promoter functions as a powerful liver-specific transcriptional enhancer (8); efficient transcription depends upon synergistic interactions between factors bound to three cis-acting elements (sites A, -214 to -192; B, -169 to -146; and C, -134 to -119) (9). The transcription factors which modulate apoA-I expression via site A or site C include members of the steroid/thyroid receptor family, RXRa (10), ARB-1 (11), HNF-4 (12), and EAR-3/COPF-TF1 (13). Depending upon the individual superfamily member, binding of these factors can result in repression or stimulation of apoA-I gene transcription. Recent evidence further suggests that repression mediated by some of these factors may play a fundamental role in switching transcription between alternative transcription activation pathways (13). The promoter context-dependent behavior of these factors underscores the importance of identifying factors that interact with site B.

In this paper we demonstrate that the hepatocyte-enriched factor HNF-3β binds to the apoA-I site B and participates in the transcriptional activation of the apoA-I gene enhancer. Our data further suggest that HNF-3β is a major determinant of the liver specificity of the apoA-I gene and that the transcriptional activity of HNF-3β is modulated by additional factors comprising the apoA-I enhancer multiprotein complex.

MATERIALS AND METHODS

Synthetic Oligonucleotides—Complementary oligonucleotides spanning the -214 to -192 (oligo A), -178 to -148 (oligo B), and -142 to -114 (oligo C) regions of the apoA-I promoter region have been described previously (9). Complementary oligonucleotides of the -110 to -85 transthyretin proximal promoter sequence (14) and the albumin eH site (eH) (15), the albumin -115 to -90 (C/EBP) (16), the class I alcohol dehydrogenase gene -10 to -1 region (17), the phosphoenolpyruvate carboxykinase promoter -416 to -402 region (18), and AB1, AB2, AB1+2, 0.5B, 1.0B, 1.5B, and 2.0B oligonucleotides were purified by polyacrylamide gel electrophoresis (19). Complementary oligonucleotides, all containing the pentanucleotide 5'-GATCT-3' at their 5' ends, were annealed and used for cloning into reporter plasmids or as competitors in the EMSA2 (see below).

Plasmid Constructions—The wild type and mutated versions of the -222 to -110 apoA-I region described previously (9) were subcloned into the BamHI site of the CAT basal promoter vector (-110CAT; 9). A synthetic HindIII-BglII oligonucleotide spanning the -41 to +7 region of the apoA-I gene was ligated into the pCI2-Basic (Promega) vector to generate the apoA-I basal promoter construct (-110Luc). The B.LUC construct was created by subcloning the -178 to -148 site B oligonucleotide (9) into the BglII site of -110Luc. The mutated apoA-I site B constructs included the following: AB1.LUC, AB2.LUC, and AB1+2.LUC in which G-cassette nucleotide substitutions were introduced in the HNF-3 B motif, B2 motif, or both B1 and B2 motifs, respectively. 0.5B.LUC, 1.0B.LUC, 1.5B.LUC, and 2.0B.LUC in which spacer lengths corresponding to half, full, one and a half, and two turns of the DNA helix, assuming 10.5 base pairs per turn, were introduced between the B1 and B2 motifs. The ABC.LUC construct was created by isolating the -222 to -110 region from the -222-110/-41Luc construct (9) by BamHI digestion.

Cell Culture and Transfections—Plasmid DNA were purified on Qiagen columns and transfected into either cultured hepatocarcinoma HepG2, monkey kidney CV-1, epithelial HeLa, or Chinese hamster ovary cells by the calcium phosphate coprecipitation method as described previously (8, 20). To correct for DNA uptake by the cells, 0.5

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The abbreviations used are: EMSA, electrophoretic mobility shift assay; CAT, chloramphenicol acetyltransferase; CMV, cytomegalovirus.
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FIG. 1. Transcription factors binding to sites A and B of the apoA-I enhancer synergistically activate gene expression. A, plasmid constructs containing the CAT gene under the control of the apoA-I core promoter (−41 to +397) with promoter sequences from the −222 to −110 apoA-I region containing nucleotide substitutions (indicated, X) that eliminate protein binding (9). B, the constructs shown in A and the apoA-I basal promoter construct (−41) were tested for CAT activity by transient transfection into HepG2 cells (see “Materials and Methods”). Each construct (5 μg) was cotransfected with pRSV-β-galactosidase plasmid (2 μg) (21) to correct for variations in DNA uptake. Relative CAT activity values represent CAT/β-galactosidase enzymatic activity ratios relative to that of the −41.CAT construct.

RESULTS

Synergistic Interactions between Transcription Factors Bound to Sites A and B Activate the apoA-I Enhancer in Liver Cells—Fig. 1 shows the results of a mutational analysis of previously defined regulatory sites in the apoA-I enhancer (9). Nucleotide substitutions designed to prevent protein binding were introduced at each site within the −222 to −110 region of the enhancer (Fig. 1A). The resulting enhancer derivatives were subcloned adjacent to the apoA-I core promoter in a CAT reporter construct whose activity was monitored upon transient transfection in HepG2 cells.

In agreement with our earlier conclusion that synergistic interactions between transcription factors bound to various regions of the enhancer control apoA-I expression levels in liver cells (9), disruption of each of the sites, individually, led to reduced transcriptional activity of the CAT reporter (Fig. 1B). The site C mutant displayed 60% of the activity of the wild-type enhancer whereas mutants in sites A and B displayed 20% and 5% of the wild-type activity, respectively. Furthermore, when enhancer derivatives carrying pairwise combinations of mutant sites were analyzed, CAT expression levels were dramatically reduced to near basal levels. Together these results suggested that the interactions between factors bound to sites A and B are primarily responsible for transcriptional activation by the apoA-I enhancer and emphasized the necessity of systematically identifying the transcription factor(s) interacting with site B.

The Hepatocyte-enriched Factor HNF-3β Binds Site B—Site B spans two nucleotide sequence motifs, CGTTGTGGCC and CTTTTTGGCC, (at positions −174 to −164 and −161 to −151, respectively) which display homology to consensus binding sites for the liver-enriched transcription factor HNF-3 (26). To assess the potential of an HNF-3 interaction with site B (or of other transcription factors exhibiting similar DNA binding...
specificity) we employed an EMSA to analyze the complexes formed on this site with HepG2 cell nuclear extracts. As shown in Fig. 2A, HepG2 nuclear extracts yielded distinct complexes with a site B probe (lane 1) which could be eliminated with an excess of unlabeled site B oligonucleotide (lane 2) but not site C oligonucleotide (lane 4). The predominant, low mobility site B complex could also be competed by oligonucleotides containing the following well-characterized HNF-3 binding sites: 1) eH site from the serum albumin liver-specific enhancer (lane 5) (15); and 2) the –110 to –85 segment of the transthyretin proximal regulatory region (lane 6) (14). The minor, high mobility complex which could be competed by site B oligonucleotide (lane 3) probably represented a novel site B protein complex devoid of HNF-3 (see “Discussion”).

No competition was observed with oligonucleotides containing transcription factor binding sites which are reminiscent of site B sequences but for which no HNF-3 interaction has been reported. These include: C/EBP (lane 7) (16); NF-kB (lane 8) (27); NF1 (lane 9) (28); OCT-1 (lane 10) (29); and alcohol dehydrogenase-ED site (lane 12) (17). However, an oligonucleotide derived from the –416 to –402 segment of the phosphoenolpyruvate carboxykinase gene promoter (18) could act as a weak competitor. This region of the phosphoenolpyruvate carboxykinase promoter has been identified as an insulin response ele-
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Fig. 3. Increasing concentrations of exogenous HNF-3β results in an increase in transcriptional activity of the construct B.LUC. The reporter constructs -41.LUC and B.LUC (0.5 µg) were tested for luciferase activity by transient cotransfection into HepG2 cells with increasing concentrations of the pCMV.HNF-3β (22) or the vector pCMV lacking the HNF-3β insert. Luciferase activity values were corrected by measurements of β-galactosidase activity generated from cotransfected pπSV-β-galactosidase. Relative fold-increase represents B.LUC luciferase activity in the presence of pCMV.HNF-3β (minus the corresponding -41.LUC values) over that observed with the pCMV vector.

ment (18) and the transcription factor binding to this site may potentially be a member of the HNF-3 family.

Presence of HNF-3 polypeptide in the EMSA complexes shown in Fig. 2A was confirmed by supershifting with an HNF-3β antibody. Addition of HNF-3β antibody to the EMSA binding reaction resulted in a supershift of the predominant complex (Fig. 2B, lane 2) accounting for the majority of the protein binding to site B. Contrary to earlier predictions of a potential C/EBP involvement in apoA-I gene regulation via site B (9, 30), addition of antibodies against members of the C/EBP family (C/EBP-α, C/EBP-β, or C/EBP-γ) had no detectable effect (lanes 4–6) on the site B complex (see “Discussion”). Finally, HNF-3β protein expressed in vitro was shown to bind to site B with high affinity and specificity (Fig. 2C, compare lane 1 with lanes 2 and 3). These results strongly implicated HNF-3β as a component of the multiprotein complex assembled at the apoA-I enhancer.

Site B Mediates Transcriptional Activation by HNF-3β—To demonstrate that HNF-3β binding to site B influences transcriptional activity of the apoA-I promoter, we monitored the activity of a luciferase reporter construct (B.LUC) (Fig. 4A), containing site B cloned adjacent to the apoA-I core promoter, in the presence of a cotransfected HNF-3 expression vector. In the absence of exogenous HNF-3 expression, the construct B.LUC displayed near basal activity (Fig. 3). A linear increase in the activity of the construct B.LUC in response to an increasing dose of the HNF-3 expression vector was observed. At saturation, transcriptional activation of the reporter construct exceeded 35-fold over the basal promoter construct (-41.LUC). Note also that the basal promoter construct (-41.LUC) reproducibly demonstrated a 2-fold increase in transcriptional activity in response to HNF-3β (Fig. 4B). This nonspecific elevation, also reported for a transthyretin core promoter reporter construct (22), may be explained by titration of inhibitory proteins by exogenous HNF-3.

Stimulation of transcription by exogenous HNF-3 in this experiment, despite the presence of HNF-3 proteins in HepG2 cells (Fig. 2B), could be attributed to limiting amounts of the factor in cultured cells (31, 44). At this endogenous concentration of HNF-3, binding to site B may not be favored. Indeed, conversion of the HNF-3 binding region to two perfect repeats, analogous to the rat apoA-I site B sequence (7), conferred endogenous transcriptional activity to the B.LUC construct (data not shown). Together with the data from the EMSA (Fig. 2), these studies unequivocally establish a role for HNF-3 in transcriptional activation of the apoA-I promoter via site B.

HNF-3β Binds Cooperatively to Site B—To define the HNF-3 cognate sequences in site B more precisely and to evaluate their relative contribution to HNF-3-dependent transcriptional activation, the two putative HNF-3 elements designated B1 and B2 were mutated either singly or in combination (Fig. 4A). The resulting mutant luciferase reporter constructs ΔB1.LUC, ΔB2.LUC, and ΔB1+2.LUC were cotransfected with 10 ng of the HNF-3β expression vector (see Fig. 3). At this concentration, the transcriptional activity of the wild-type B.LUC construct was approximately 13-fold above that of the -41.LUC construct (Fig. 4B). Mutations in either the B1 or B2 motif affected HNF-3-dependent transactivation with the B1 mutation being more severe. The double mutant construct ΔB1+2.LUC was unresponsive to exogenous HNF-3. In EMSA experiments, the binding affinity of in vitro expressed HNF-3β for the wild-type site B oligonucleotide greatly exceeded its affinity for either HNF-3 motif alone (Fig. 4C). The B2 motif was a higher affinity HNF-3β binding site than the B1 motif and as anticipated, mutations in both sites abolished HNF-3β binding. Furthermore, measurements employing mutant oligonucleotides to compete the HNF-3 complex formed on site B indicated that both B1 and B2 motifs were required for efficient complex formation (Fig. 4D). These results suggested that cooperative interactions between HNF-3 moieties bound at each of the elements are required for maximal occupation of site B by HNF-3 and for transcription activation.

To ascertain whether the proximity per se of the two site B elements or their relative stereo-specific alignment was critical for the activation potential of HNF-3, spacer-length variants of site B were created by introducing half- or full-helical turns between B1 and B2. As shown in Fig. 4E, the introduction of a half-helical turn (0.5B.LUC) or full-helical turn (1.0B.LUC) disrupted HNF-3β-dependent transcriptional synergism. All activity was lost upon introduction of two full-helical turns (2.0B.LUC) even though both HNF-3 motifs were intact. Therefore, these results suggested that site B is a uniquely optimized HNF-3 response element, wherein HNF-3 cooperative binding and transcriptional synergism are dependent upon the spatial distribution of the two elements unlike what has been reported for other sites (32).

HNF-3β and HNF-4 Activate the ApoA-I Enhancer in Nonhepatic Cells—Given the restriction of apoA-I gene expression to the liver and intestine (4–7), and the identification of site B in the liver-specific enhancer as a potent HNF-3 response element, we wondered if this liver-enriched transcription factor would suffice to activate transcription through site B in nonhepatic cells. For this purpose, the reporter construct B.LUC, together with the HNF-3 expression vector, were transiently transfected into the hepatic HepG2 cell line or the nonhepatic CV-1, HeLa, and Chinese hamster ovary cell types. As shown in Fig. 5A, each of the nonhepatic cell types was capable of eliciting enhanced transcriptional activity in response to exogenous HNF-3β. While the HNF-3 dependent activation was low in HeLa and Chinese hamster ovary cells, the activation levels observed in CV-1 cells approached those in HepG2 cells. These results implied that given an optimal DNA-binding site, additional liver-specific factors may not in fact be required for activity of HNF-3 in contrast to conclusions reached in earlier reports (22, 33). Since the natural context of site B in the enhancer region subjects it to a variety of influences (3, 6,
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Fig. 4. HNF-3β protein binds cooperatively to the apoA-I promoter site B. A, plasmid constructs containing the wild-type apoA-I site B (B.LUC) or oligonucleotides with substitutions in either the B1 motif (ΔB1.LUC), B2 motif (ΔB2.LUC), or both motifs (ΔB1+2.LUC) (bracketed). B, mapping of the HNF-3β binding site within the apoA-I promoter site B. The wild-type site B construct, B.LUC, and nucleotide substituted constructs ΔB1.LUC, ΔB2.LUC, and ΔB1+2.LUC were tested for luciferase activity by transient cotransfection assays as described in the legend to Fig. 3. 10 ng of pCMV.HNF-3β (+) or pCMV (-) were used for these experiments. Relative luciferase activity values represent luciferase/β-galactosidase enzymatic ratios relative to that of -41.LUC construct. C, cooperative binding of in vitro translated HNF-3β to the apoA-I promoter site B, EMSA experiments were performed as in Fig. 2C. The oligonucleotide probes included wild-type site B (lane 1) or the mutant derivatives (as in A): ΔB1 (lane 2), ΔB2 (lane 3), and ΔB1+2 (lane 4). D, HNF-3β was incubated with increasing amounts of unlabeled oligonucleotides B (lanes 1-4), ΔB1 (lanes 5-7), ΔB2 (lanes 8-10), or ΔB1+2 (lanes 11-13) before addition of wild-type site B probe. 10-fold (lanes 2, 5, 8, and 11), 50-fold (lanes 3, 6, 9, and 12), or 100-fold (lanes 4, 7, 10, and 13) molar excess of each competitor were added. E, effect of altering the spacing between HNF-3 binding elements B1 and B2 of apoA-I site B. Derivatives of reporter construct B.LUC containing additional nucleotides between B1 and B2 were tested for HNF-3β-dependent transcriptional activity as described in the legend to Fig. 3. The spacer-length derivatives included 0.5B.LUC (half-helical turn), 1.0B.LUC (one helical turn), 1.5B.LUC (one and a half helical turns), and 2.0B.LUC (two helical turns). Relative luciferase activity values were processed as in B.

34–36) and in view of reports indicating that HNF-3 functions in coordination with heterologous transcription factors (15, 37–41), we examined the ability of HNF-3 to activate transcription via the intact apoA-I enhancer. For this purpose, the response to exogenous HNF-3 from a luciferase reporter construct ABC.LUC containing the -222 to -110 region of the apoA-I enhancer in HepG2 cells was assessed (Fig. 5B). In HepG2 cells, this construct displayed constitutively elevated activity (about 100-fold over that of a core promoter reporter construct). By contrast, only basal level expression of the construct is detectable upon transfection into CV-1 cells in agreement with our previous reports (8, 9), demonstrating cell-type specificity of the apoA-I enhancer. Cotransfection of reporter construct ABC.LUC with HNF-3 expression vector had a minor
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**DISCUSSION**

Organization of transcriptional enhancers into distinct modules (reviewed in Ref. 1) facilitates formation of a functional multiprotein complex that serves to integrate signals borne by each of the factors involved. Thus, since apoA-I gene transcription is known to be influenced by diverse stimuli (6, 7, 34–36, 42, 43), the apoA-I enhancer can reasonably be expected to incorporate modular mechanisms to respond to these signals.

To begin to unravel the multifarious interactions which constitute apoA-I transcription control, we have been systematically cataloging the transcription factors involved in liver-specific expression of its gene. The list of transcription factors hitherto implicated in transcription control by the apoA-I liver-specific enhancer includes the following: ARP-1 (11), EAR3/COPP-TFI (13), RXRa (10), HNF-4 (12, 13), Egr-1 (13), and C/EBP (15). In this work we present evidence for the involvement of HNF-3P as well. HNF-3P belongs to a family of liver-enriched transcription factors that are related to the Drosophila homeotic gene product, forkhead (22). HNF-3P proteins have been shown to participate in the regulation of a number of liver-specific genes including transthyretin (14), albumin (15), and apolipoprotein B (44). While it is by no means exhaustive, our list already reflects a potential for combinatorial association between liver-enriched (e.g., HNF-3, C/EBP, and HNF-3) and ubiquitous (ARP-1, EAR-3, and RXRa) transcription factors as has been reported for transcription of other liver-specific genes (2).

The detailed structural organization of an HNF-3-containing apoA-I enhancer complex remains to be elucidated. Based on the critical nature of site B deduced by our mutational analysis (Fig. 1 and Ref. 9) as well as our ability to reconstitute apoA-I enhancer activity in nonhepatic cells by HNF-3 and HNF-4 (see below), we postulate that HNF-3 (and other factors interacting with site B) plays a dominant role in potentiating the assembly of the multiprotein complex. Other components of the complex would presumably include HNF-4 or another member(s) of the steroid/ thyroid hormone receptor superfamily interacting with sites A and C. Modeling the apoA-I system on other well-characterized enhancer complexes (45), it is also tempting to speculate that initial HNF-3 binding facilitates subsequent interactions manifested as the observed synergism in transcription activation. This event may be facilitated by altering the DNA conformation within the enhancer (1). Intriguingly, DNase I footprinting of the enhancer revealed hypersensitive sites around site B (9, 11), diagnostic of gross DNA conformational changes and consistent with the ability of HNF-3 to bend DNA (33, 41, 46–48).

In view of the continual environmental changes to which the apoA-I regulatory apparatus is exposed, and unlike other multiprotein enhancer assemblies (e.g., T cell receptor alpha gene (45)), the exact composition of the apoA-I enhancer complex is predicted to vary at any given point in time (13). We have previously suggested that an ARP-1-induced repressed state may reflect passage through an obligatory intermediate which facilitates transcription factor exchange on the enhancer in the switch from one activated state to another. Thus, while our current data ascribe a critical role to HNF-3 in apoA-I transcription control we also imagine situations where an HNF-3 requirement may be entirely by-passed. Indeed, the inability of HNF-3 antibodies to quantitatively supershift the complexes formed by HepG2 nuclear extracts on site B (Fig. 2B) may be interpreted in terms of a subpopulation of complexes lacking HNF-3. Similarly, while we were unable to supershift this com-
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plex with C/EBP antibodies we have previously observed discrete C/EBP effects on apoA-I transcription (13), suggesting that the extracts used in the present experiment were not enriched for a C/EBP-containing subpopulation.

Site B, unlike other cognate sites for HNF-3 (22, 33), efficiently supports HNF-3 mediated activation (in both hepatic and nonhepatic cell types) when placed close to core promoter elements. However, in CV-1 cells, the natural location of site B within the context of the enhancer renders HNF-3 dependent upon synergistic interactions with transcription factors from other families. Since sites A and C which flank site B can be occupied by factors other than HNF-4 in CV-1 cells, it was surprising that activation of an otherwise silent transcription unit could be readily achieved simply by limiting quantities of a subset of nonhepatic cells results from limiting quantities of a subset of liver-enriched factors in these cells. Nevertheless, in nonhepatic cells, Costa for providing the HNF-3 antibody and the HNF-3p.CMV expression vector, E. Ferris and N. Papanicolaou for technical assistance, and N. Stapleton and J. Vallancourt for helping with the figures.

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