A Broad Role for the Zinc Finger Protein ZNF202 in Human Lipid Metabolism*

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The ZNF202 gene resides in a chromosomal region linked genetically to low high density lipoprotein cholesterol in Utah families. Here we show that the ZNF202 gene product is a transcriptional repressor that binds to elements found predominantly in genes that participate in lipid metabolism. Among its targets are structural components of lipoprotein particles (apolipoproteins AIV, CIII, and E), enzymes involved in lipid processing (lipoprotein lipase, lecithin cholesteryl ester transferase), and several genes involved in processes related to energy metabolism and vascular disease. Based on the linkage and apparent translational function of ZNF202, we propose that ZNF202 is a candidate susceptibility gene for human dyslipidemia.

Familial hypoalphalipoproteinemia (HA),1 the most common form of decreased plasma HDL levels, is an independent risk factor for early coronary disease (1). HDL contains apolipoproteins AI and AII as its major protein components and various amounts of triglycerides, phospholipids, and cholesterol esters. Its primary function appears to be the “reverse transport” of cholesterol from peripheral tissues to the liver, where it is catabolized into bile acids. A second proposed function for HDL is the uptake of apolipoproteins and free cholesterol from catabolized very low density lipoproteins and chylomicrons.

Phenotypic variation of plasma HDL levels depends on both genetic and environmental factors such as exercise. About 50% of HDL variation is ascribed to genetic influences (2). A number of rare mutations have been described that result in severely depressed HDL levels, among them mutations in the genes encoding apolipoprotein AI, apolipoprotein B, lecithin-cholesterol acyltransferase, and lipoprotein lipase (LPL) (3). Recently, ATP binding cassette transporter-1 was identified as the gene underlying Tangier disease, an extremely rare form of HA (4–7). Although these rare deficiencies account only for a fraction of individuals with lipid abnormalities, their existence suggests that less severe dyslipidemic phenotypes may be due more subtle disruptions in the expression and function of genes that participate in lipid metabolism.

In an effort to discern other genetic contributors to HA, we performed linkage analysis on large Utah pedigrees that have heritable HA and a family history of early coronary disease. A locus on human chromosome 11q23, clearly distinct from the apoAI/CII/AIV gene cluster, is linked to HA in many Utah families.2 One of the genes localized to this region is the zinc finger transcription factor ZNF202 (9). In light of the increasingly recognized role of transcription factors in contributing to the transcription of multiple genes in lipid-related pathways (10, 11), we characterized the biochemical function of ZNF202. This analysis reveals that ZNF202 is a transcriptional repressor that binds to the regulatory region of many genes involved in lipid metabolism. ZNF202 thus joins a growing number of transcription factors acting in metabolic coordination.

EXPERIMENTAL PROCEDURES

Cell Culture and Antibodies—HepG2 and HEK293 cells were obtained from ATCC (HB-8065 and CRL-1573, respectively) and grown in Dulbecco’s modified Eagle’s medium supplemented with 10% fetal calf serum. A glutathione S-transferase (GST) fusion protein of amino acids 1–199 of ZNF202 was purified from bacterial extracts and used to generate polyclonal antibodies in rabbits. Antisera were affinity-purified on a GST-ZNF202 column.

In Vitro Protein Expression—cDNAs representing the alternatively spliced mRNAs of ZNF202 were cloned into pcDNA3.1 (Invitrogen). Proteins were synthesized and [35S]methionine-labeled in vitro using a coupled transcription/translation system (Promega).

Affinity Purification of GST-ZNF202—A GST fusion with ZNF202 zinc fingers 3 through 8 (GST.ZF3.8) was generated by inserting amino acids 474 to 648 of ZNF202 into pGEX-4T-3 (Amersham Pharmacia Biotech). GST.ZF3–5 protein was expressed in BL21 cells and purified essentially as described by the manufacturer. For gel shift assays, protein was eluted from glutathione-Sepharose and dialyzed to remove residual glutathione. Protein concentration was estimated from Coomassie Blue-stained SDS-polyacrylamide gels.

Affinity Selection of Binding Sites—An affinity selection procedure was modified from a method described previously (12). An oligonucleotide designated INVLIN236 (5′-ACC CGA ATT CGG ATC C (N) 36 CG 9′-ACC CGA ATT CGG ATC C) was synthesized with a 36-nucleotide random sequence between defined sequences at the 5′ and 3′ ends. GST.ZF3.8 was immobilized on GSH-agarose beads (Amersham Pharmacia Biotech) and pre-blocked with 200 ng/ml poly(dI-dC) for 30 min in 1× GSA buffer (25 mM Hepes pH 7.5, 10 mM ZnCl2, 10% glycerol, 5 mM dithiothreitol, 5 mM MgCl2, 50 mM KCl, 0.65% Triton X-100). This affinity matrix was used to select specific sequences from the pool of random oligonucleotides. Oligonucleotides were added to the GST-ZNF202 agarose beads for 30 min at 22 °C in 1× GSA buffer. Unspecifically retained oligonucleotides were washed away with GSA buffer.

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removed by stepwise washes with 3 bed volumes of 1× GSA buffer containing increasing amounts of NaCl (0.1 M and 0.2 M). In the first round, a low and a high stringency-bound fraction were obtained by collecting sequential elutions at increasing salt concentrations. The low salt-bound fraction was obtained by eluting with 0.3 M NaCl. After two more washes at 0.3 M and 0.5 M, a high salt fraction was collected from an elution with 0.6 M NaCl. Both pools were submitted to additional cycles. Subsequent elutions were performed with 0.3 M for the low stringency pool and 0.6 M for the high stringency fraction. From each of the affinity purification rounds, the oligonucleotide pools were amplified for 22–24 cycles with the primers 5′-ACC GAC TGG TGC GAC TCA-3′ and 5′-TCT GCT GAA TCT CTA-3′ in the following PCR protocol: 96 °C for 4 s, 62 °C for 10 s, and 72 °C for 30 s. After the fifth iteration of selection, the pools of selected oligonucleotides were cloned into pBluescript for sequence analysis.

**Gel Mobility Shift Assays**—Gel mobility shift assays were carried out using purified bacterially expressed GST.ZF.3 protein or in vitro transcribed and translated ZNF202 (amino acids 304–645). Gel-purified promoter fragments were end-labeled with polynucleotide kinase and [γ-32P]ATP. Approximately 2 ng of GST.ZF.3 and 20 fmol of end-labeled DNA were incubated for 20 min at 22 °C in 1× GSA buffer in a final volume of 15 μl. Complexes were resolved on a 5% non-denaturing polyacrylamide gel in 0.5× Tris-borate EDTA and visualized on a PhosphorImager (Molecular Dynamics, Sunnyvale, CA). Gel shift probes were generated by nested polymerase chain reaction from genomic DNA with the same primers amplifying the following promoter regions (numbering according to listed GenBank® references): apolipoprotein AIV, X13368, nt 779–1187; apolipoprotein CHI, X13367, nt 675–1052; apolipoprotein E, M10065, nt 723–1062; hepatic nuclear factor 4, U72959, nt 558–1053; lipoprotein lipase, M29649, nt 199–544; lecithin-cholesterol acyltransferase, X51966, nt 1411–1767; phospholipid transfer protein, U38950, nt 310–446; hepatic triglyceride lipase, X58779, nt 500–800; vascular endothelial growth factor, M63971, nt 1193–1348; insulinoma-accession numbers whose annotations included the key words “exon1,” “promoter,” “regulator,” or “upstream.” More than 7300 human accessions were scanned using all combinations of the accession numbers. Analysis of 55 clones revealed that 5′-non-coding elements, we performed electromobility shift assays with promoter fragments that include the presumed ZNF202 promoter. As shown in Fig. 4, A and B, motifs show significantly higher similarity to C2H2 fingers known to bind DNA than do fingers three through six (14). The central part of the protein is occupied by a Krueppel-associated box (KRAB). KRAB domains, present in one-third of all zinc finger proteins, mediate transcriptional repression through mobilization of a corepressor, for example KAP-1(15–17). The N terminus contains a SCAN (or LeR) motif, a suggested protein interaction module, observed in other zinc finger proteins (18). Further analysis of the protein sequence by PESTFIND (19) reveals extensive PEST sequences that suggest a rapid protein turnover, similar to that observed for several other transcription factors. The conceptual translation (GenBank® accession AF027218) of the second common splice form, m3 (ZNF202m3), predicted a N-terminal-truncated protein that retains the KRAB domain and the eight C-terminal zinc finger motifs. However, expression of a ZNF202 m3 cDNA revealed that the m3 form encodes a truncated ZNF202 protein of 142 amino acids encompassing only the SCAN domain. Expression of the m1 and m3 gene products was demonstrated by both coupled transcription/translation experiments and transient transfections in HEK293 cells followed by SDS-PAGE and immunoblots (Figs. 1, B and C). If, as has been suggested (18), SCAN domains mediate dimerization, the m1 and m3 gene products may interact with each other and potentially with other SCAN domain-containing proteins.

Northern blots containing a wide range of tissues and several cell lines were probed with ZNF202 cDNA to determine its expression pattern. Maximal expression was detected in heart, lung, liver, and testis (Fig. 2).

**RESULTS**

**Structural Features of ZNF202**—The ZNF202 gene contains 10 exons spanning 27 kilobases of chromosome 11. It was independently cloned as a candidate gene for predisposition to breast and lung cancer (9). Cloning of ZNF202 cDNAs (GenBank® accession numbers AF027219 and AF027218) revealed a number of alternative splices in the 5′-non-coding region and two common splice variants in the coding region named ZNF202m1 and ZNF202m3 (Fig. 1A). The full-length m1 form (ZNF202m1) encodes a predicted 648 amino acid protein with several conserved domains. The C terminus encodes eight consecutive C2H2 zinc finger motifs; the first, second, seventh, and eighth C2H2 motifs show significantly higher similarity to C2H2 fingers known to bind DNA than do fingers three through six (14). The central part of the protein is occupied by a Krueppel-associated box (KRAB). KRAB domains, present in one-third of all zinc finger proteins, mediate transcriptional repression through mobilization of a corepressor, for example KAP-1(15–17). The N terminus contains a SCAN (or LeR) motif, a suggested protein interaction module, observed in other zinc finger proteins (18). Further analysis of the protein sequence by PESTFIND (19) reveals extensive PEST sequences that suggest a rapid protein turnover, similar to that observed for several other transcription factors. The conceptual translation (GenBank® accession AF027218) of the second common splice form, m3 (ZNF202m3), predicted a N-terminal-truncated protein that retains the KRAB domain and the eight C-terminal zinc finger motifs. However, expression of a ZNF202 m3 cDNA revealed that the m3 form encodes a truncated ZNF202 protein of 142 amino acids encompassing only the SCAN domain. Expression of the m1 and m3 gene products was demonstrated by both coupled transcription/translation experiments and transient transfections in HEK293 cells followed by SDS-PAGE and immunoblots (Figs. 1, B and C). If, as has been suggested (18), SCAN domains mediate dimerization, the m1 and m3 gene products may interact with each other and potentially with other SCAN domain-containing proteins.

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**ZNF202 Binds Specific Promoter Elements**—The protein motifs observed in the ZNF202 m1 gene product imply that it functions as a DNA-binding protein and as a transcriptional regulator. Fluorescent microscopy of HEK293 cells expressing green fluorescent protein-ZNF202m1 fusions reveals a strong nuclear fluorescence (data not shown), as expected for a transcription factor. To define a DNA binding site for ZNF202m1, we employed a GST fusion protein containing the last six zinc fingers of ZNF202 m1 (GST.ZF3–8) to select a consensus binding site from a complex mixture of random oligonucleotides (12). After five rounds of selection and amplification, the bound fraction was cloned and sequenced. Analysis of 55 clones revealed a simple consensus binding motif (5′-GGGTGTT-3′), as shown in Fig. 3A. The rules of Chou and Klug (20) predict that they essentially the same binding specificity for these zinc fingers. Direct repeats of the selected motif were found in the apoAIV and apoCIII promoters (Fig. 3B); this enhancer affects the expression of the entire apoAI/CHI/AIV gene cluster. To confirm that GST.ZF3–8 binds the predicted elements, we performed electromobility shift assays with promoter fragments of apoAIV and apoCIII. As shown in Fig. 4, A and B, promoter fragments that include the presumed ZNF202 site were bound by GST.ZF3–8. Subdivision of the apoCIII and...
apoAIV probes into smaller fragments revealed that fragments containing the consensus repeat were bound by GST.ZF3–8, whereas adjacent fragments lacking the consensus site were not bound. Also, several non-related DNA fragments derived from the promoters of heat shock protein 90 and glycerol-3-phosphate hydrogenase were negative for binding by GST.ZF3–8. Methylation interference experiments indicated that GST.ZF3–8 binds to the predicted sequence elements (data not shown). To demonstrate binding specificity, we performed a competition assay. Fig. 4C shows binding of ZNF202 to a fragment of the β3-adrenergic receptor promoter containing a predicted ZNF202 binding site. The addition of a 50× excess of the cold β3-adrenergic receptor promoter fragment effectively competed for binding to the labeled β3-adrenergic receptor probe. A negative control fragment of the neurofibromin promoter did not compete under identical conditions. Protein dilution experiments suggested the binding of GST.ZF3–8 to the apoAIV DNA fragment has an apparent $K_d$ of approximately 10 nM, an upper limit value that assumes that all purified GST.ZF3–8 is in an active conformation. This binding constant is similar to the apparent $K_d$ described for other zinc finger proteins (21). We thus conclude that binding of GST.ZF3–8 to these promoter fragments is sequence-specific.

To identify other possible target promoters, we generated a

FIG. 1. Alternately spliced transcripts of ZNF202. A, genomic structure and alternative splices of ZNF202. Ten exons are parsed over 27 kilobases of genomic DNA. Exons containing coding sequence are shown as open boxes, and non-coding exons are shaded. Conserved protein domains are indicated by their motif names. The alternative splice between exons 5 and 6, giving rise to different protein products, is detailed below. Capital letters indicate exon sequence, and small letters are intron sequence. The reading frame is marked by nucleotide triplets. The m3 open reading frame terminates at the start of exon 6. B, coupled in vitro transcription/translation was performed in the presence of [35S]methionine using a cDNA template corresponding to the m1 or m3 splice form of ZNF202. The reaction product was run on SDS-PAGE, dried, and subjected to autoradiography. C, immunoblot of ZNF202 m1 and ZNF202 m3 expressed in cell culture. Mammalian expression constructs corresponding to the m1 and m3 forms were introduced into HEK293 cells by cationic lipid-mediated transfection. After 48 h, the cells were lysed in radioimmunoprecipitation assay, run on SDS-PAGE, transferred to nitrocellulose, and identified in an immunoblotting procedure with a ZNF202 SCAN domain-specific rabbit antibody.

FIG. 2. Expression pattern of ZNF202. A, multi-tissue Northern blots probed with ZNF202 cDNA. Membranes were obtained from CLONTECH and hybridized with a cDNA probe containing nucleotides 219–969 of the ZNF202 cDNA. Membranes were stripped and reprobed with a glycerol-3-phosphate dehydrogenase probe to verify equal loading. Molecular size markers are given in kilobases. B, tumor cell line blot probed with ZNF202 cDNA as described in A. PBL, peripheral blood leukocytes.

FIG. 3. DNA binding preference of ZNF202 zinc fingers. A, results of the binding site selection with GST.ZF3.8. Oligonucleotides from the fifth round of selection were cloned and sequenced. The frequency of bases in an alignment of 55 clones is shown in the upper portion of the table. The consensus binding motif is underlined. B, occurrence of the consensus binding site in the apoAIV, apoCIII, and LPL promoters. The apoAIV sequence corresponds to base pairs 779 to 1187 of GenBank accession X13368, apoCIII to base pair 675 to 1052 of X13367, and LPL to base pair 296 to 329 of M29549.
Results of bioinformatic survey for ZNF202 binding sites

The informatics search for ZNF202 binding sites in promoters was performed as follows. Twenty-one promoters were identified with homologous sequences in their promoters; 17 of these were tested in EMSAs and were confirmed to bind GST.ZF3–8. Three additional promoters (apoE, lecithin-cholesterol acyltransferase (LCAT), and HNF4α) were identified in less stringent searches and were confirmed in a similar manner, thus yielding the 20 EMSA-positive promoters shown in the table. Additionally, several control promoter fragments lacking sequences similar to the consensus site (heat shock protein 90, glycerol-3-phosphate dehydrogenase, and NFI*) were employed in EMSAs and were found not to bind ZNF202m1 derivatives. Results from transient transfection assays in HepG2 cells were given in the column labeled “Repression Function.” The ranges of the DNA fragments used are given under “Experimental Procedures,” with 32P-end-labeled fragments (heat shock protein 90, glycerol-3-phosphate dehydrogenase, and NFI*) employed.

| Gene        | Repression | Function of gene product                  |
|-------------|------------|------------------------------------------|
| apoAIV      | Yes        | Lipoprotein structural component         |
| apoCIII     | Yes        | Regulates expression of apoAIV/CIII/AIV gene complex |
| apoE        | Yes        | Lipoprotein structural component         |
| HNF4        | Yes        | Hepatic ligand-activated transcription factor |
| LPL         | ND         | Lipid metabolism                         |
| LCAT        | ND         | Lipid metabolism                         |
| PLTP        | Yes        | Lipid metabolism                         |
| HTGL        | ND         | Lipid metabolism                         |
| VEGF        | ND         | Endothelial cell growth factor            |
| IA-1        | ND         | Zinc finger transcription factor, neuroendocrine tumor antigen |
| β3AR        | ND         | Signaling receptor implicated in metabolic diseases |
| CRABP2      | ND         | Retinoic acid signaling                   |
| CALRT1      | ND         | Calcium signaling                        |
| GOS24       | ND         | Zinc finger transcription factor, cell cycle control |
| p16/ALT     | ND         | Cell cycle control                       |
| PNMTA       | ND         | Hormone synthesis                        |
| PLP         | ND         | Myelin component                         |
| PILOT       | ND         | Zinc finger transcription factor, growth response |
| NFI*        | ND         | Signaling                                |
| LAG3        | ND         | Lymphocyte signaling receptor             |

Table I

custom unbiased data base of known human promoters from GenBank entries through a keyword search. These sequences were searched with the consensus binding motifs found in the apoAIV and LPL promoters or in the apoCIII enhancer, which had been shown to bind ZNF202 zinc fingers in vitro. Remarkably, the motif appeared in only a small number of promoters (Table I). Moreover, the majority of the genes identified are known to be involved in lipid metabolism or to be associated with metabolic disorders. We amplified most of these putative elements from genomic DNA and used them as probes in gel shift experiments to confirm ZNF202 binding. These results are summarized in Table I, and an alignment of the binding sites is displayed in Fig. 5. Notably, several of our binding elements coincide with sites previously mapped as DNA-protein interaction sites (11). For example, the ZNF202 site in the apoCIII promoter overlaps with an element at -611 to -592.
relative to the transcription initiation site (Fig. 4a); this element is thought to bind Sp1 and an unidentified factor CIII1 from rat liver (11), and the rat ortholog to ZNF202 may be that factor.

ZNF202 Transcriptional Activity—Having established that ZNF202m1 zinc fingers bind DNA in a sequence-specific manner, we next analyzed the effect of full-length ZNF202m1 on transcription from target promoters. The presence of a KRAB domain suggested that the ZNF202m1 gene product acts as a transcriptional repressor (15–17). To test this hypothesis, we used several reporter constructs containing portions of the apoE and apoAIV genes; these fragments all had been shown to bind ZNF202 in gel shift experiments. The reporter constructs were introduced by transfection into HepG2 human hepatoma cells with varying amounts of a ZNF202m1 expression plasmid. Reporter gene expression was measured in two independent systems by monitoring either secreted alkaline phosphatase (SEAP) or luciferase activity. As shown in Fig. 6, co-expression of ZNF202 represses transcription from the apoAIV and apoE reporter constructs 5–10-fold relative to the transcriptional activity in the absence of ZNF202. This repression is dose-dependent. No effect was observed for a control plasmid lacking a ZNF202 binding site. Identical results were obtained using a luciferase reporter (data not shown). Additional fragments derived from the promoters of phospholipid transfer protein and hepatic nuclear factor-4 (HNF4) and the apoCIII enhancer that had been shown to bind GST.ZF3–8 in vitro were also used in reporter assays. Transcriptional repression in the presence of ZNF202 was similar to the one observed for the apoE and apoAIV promoters (Table 1).

DISCUSSION

Our results establish that ZNF202 is a transcriptional repressor that can bind in vitro to the regulatory regions of a large number of genes related to lipid processing. The target genes of ZNF202 can be divided into three distinct classes. The first group contains genes that encode structural components of lipoprotein particles: apoAIV, apoCIII, and apoE. Additionally, through its action on the apoCIII enhancer, ZNF202 also affects transcription of the apoA1 gene (11). A second class comprises enzymes involved in lipid processing: LPL, lecithin-cholesterol acyltransferase, and hepatic triglyceride lipase. Members of these first two groups are essential for maintaining lipid and cholesterol homeostasis. The overall effect of ZNF202 on lipid metabolism is difficult to predict because several of the genes products are thought to have counterbalancing functions. For example, in our hands ZNF202 represses transcription of both apoCIII and LPL reporter gene constructs, yet under some conditions these two genes have opposite effects on triglyceride hydrolysis because apoCIII inhibits LPL (22). The third group of target genes includes several genes already suspected of contributing broadly to metabolic processes: HNF4a, insulinoma-associated gene 1, β-3 adrenergic receptor, and vascular endothelial growth factor type 1 (VEGF1), M63971 (nt 1288–1259); apolipoprotein E, M10065 (nt 305); lipoprotein lipase, M29549 (nt 297–326); β-3 adrenergic receptor (Beta3AR), M62473 (nt 1149–1178); vascular endothelial growth factor type 1 (VEGF1), M63971 (nt 1288–1259); apolipoprotein E, M10065 (nt 851–880).
also represses the expression of several other transcription factors and signaling molecules known to participate in metabolic processes (Table 1).

Expression of structural components of lipoproteins and of the enzymes that act on them likely is coordinated, and shared regulatory elements afford one mechanism by which this coordination may occur. Specifically, the liver X receptor α transcription factor binds to DR-4 sites in the promoters of genes involved in cholesterol catabolism such as cholesterol 7α-hydroxylase (8). Similarly, farnesoid X receptor orchestrates bile acid synthesis and recovery through opposing actions on the transcription of the ilial bile acid protein gene and of cholesterol 7α-hydroxylase (10). Finally, HNF4α enhances transcription of many genes related to lipid metabolism, including the genes for apoAI, apoB, apoCIII, apoAIV, and acyl-CoA dehydrogenase (11). The ZNF202 binding sites elucidated in this study constitute yet another example of a single transcription factor influencing multiple genes in a specific metabolic pathway.

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