Phosphatidylcholine (PC) is the most abundant eukaryotic phospholipid and serves critical structural and cell-signaling functions. CTP:phosphocholine cytidylyltransferase (CT) is the rate-limiting enzyme in the CDP-choline pathway of PC biosynthesis, which is utilized by all tissues and is the sole or major PC biosynthetic pathway in all non-hepatic cells. Herein, we present the complete structure of the murine CT (*Ctpct*) gene. One P1 genomic clone and six subsequent plasmid subclones were isolated and analyzed for the exon-intron organization of the *Ctpct* gene. The gene spans approximately 26 kilobases and is composed of 9 exons and 8 introns. The exons match the distinct functional domains of the CT enzyme: exon 1 is untranslated; exon 2 codes for the nuclear localization signal domain; exons 4–7 encompass the catalytic domain; exon 8 codes for the α-helical membrane-binding domain; and exon 9 includes the C-terminal phosphorylation domain. Two transcriptional initiation sites, spaced 35 nucleotides apart, were identified using 5′-rapid amplification of cDNA ends polymerase chain reaction. The 5′ natural flanking region was found to lack TATA or CAAT boxes and to contain GC-rich regions, which are features typical of promoters of housekeeping genes. Several sites that have the potential to interact with transcription regulatory factors, such as Sp1, AP1, AP2, AP3, Y1, and TFIIIA, were identified in the 5′-region of the gene and found to be distributed in two distinct clusters. These data will provide the basis for future studies on the cis- and trans-acting factors involved in *Ctpct* gene transcription and for the creation of induced mutant mouse models of altered CT activity.

Synthesis of the most abundant eukaryotic phospholipid, phosphatidylcholine (PC),‡ which serves critical structural and cell-signaling functions, involves three major enzymatic steps: phosphorylation of choline, synthesis of CDP-choline from choline-phosphate and CTP, and transfer of choline-phosphate from CDP-choline to diacylglycerol to form PC (1, 2). This pathway, called the CDP-choline, or Kennedy, pathway, is the major or sole one used by all extrahepatic tissues. PC biosynthesis in hepatocytes also occurs via this pathway, but an alternative one in which phosphatidylethanolamine is converted to PC by phosphatidylethanolamine N-methyltransferase (PEMT) is also used by this cell type (1, 2). The rate-limiting step in the Kennedy pathway is the synthesis of CDP-choline, which is catalyzed by the enzyme CTP:phosphocholine cytidylyltransferase (CT). CT cDNAs from several different species, including rat (3), mouse (4, 5), hamster (6), and human (5), have been cloned and sequenced. All of these CT cDNAs encode a CT protein of 367 amino acids, and the sequences are highly homologous among the different species.

CT exists in both soluble and nonintegral membrane-bound forms and is subject to both pre-translational (7–9) and post-translational regulation (1, 2). Post-translational regulation may involve binding of CT to membranes in cells as well as changes in C-terminal phosphorylation. In addition, CT mRNA levels increase with growth factor stimulation of certain cells (7), after partial hepatectomy in rat liver (9), and during differentiation, and there is a decrease in CT mRNA after overexpression of PEMT2 in hepatoma cells (8). Whether the changes in mRNA levels under these conditions are due to changes in CT gene transcription or to changes in CT mRNA stability (cf. Ref. 7) has not been fully investigated. Importantly, all of these regulatory studies have been conducted *in vitro* or in cultured cells, and, in a few cases, results obtained from different laboratories have been contradictory. Thus, the physiological regulation of CT activity, particularly *in vivo*, is an important area for further investigation.

Our laboratory has recently become interested in the physiology and regulation of CT during atherogenesis (10–12). We found that free cholesterol loading of macrophages, an important event in advanced atherosclerosis, leads to the induction of CT activity, PC biosynthesis, and PC mass (10, 11). This response helps the macrophages adapt to potentially toxic levels of cellular free cholesterol, and failure of this response may be one cause of an important leisional event, namely macrophage necrosis (12). To test these ideas *in vivo* using induced mutant mouse models, it became necessary for us to determine the structure of the murine CT, or *Ctpct*, gene. This information should also be useful in addressing some of the uncertainties
based on the results of the Southern blot. Clone No. 4904 was then the P1 clones, No. 4904, contained the entire Technologies, Inc.) following the protocol of the manufacturer. One of sequencer ( Applied Biosystems/Perkin-Elmer model 373A) in the DNA DNA preparation kit following the protocol of the manufacturer. DNA in binding transcriptional factors. DNA was prepared using the Qiagen gion of clone 6 was sequenced to identify potential sequences and exon-intron boundaries. In addition, the 5 regarding pre- and post-translational CT regulation described above. Given the central importance of CT, it is surprising that only a small part of the structure of the Ctpct gene has been reported thus far (4). Herein, we present the complete structure of the murine Ctpct gene, which reveals a relationship between exon organization and functional domains of CT, the existence of two transcriptional initiation sites, and the presence of several potential 5’-upstream cis-elements that may be involved in gene transcription.

EXPERIMENTAL PROCEDURES

Materials—All chemical reagents were purchased from either Sigma or Fisher. All restriction endonucleases and other enzymes from New England Biolabs (Beverly, MA). The [α-32P]dCTP (DuPont) was purchased from DuPont NEN. The random primer labeling kit, the 32P-labeled 5’-elements involved

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dures,” four clones were isolated from a murine 129/J stem cell genomic DNA library in the P1 vector, and one of these genomic clones (No. 4904) was found to contain the entire Ctpct gene by Southern blot using various CT cDNA probes (Fig. 1). Clone No. 4904 was digested by either EcoRI or PstI and subcloned into pBluescript KS1 vector. Six subclones encompassing parts of the Ctpct gene were identified by Southern blot analysis, and these subclones were sequenced. As shown in Fig. 1, clone 1 (2 kb) contains the 3’9 portion of intron I and the 5’9 portion of exon 2; clone 2 (3 kb) contains the 3’9 portion of intron I, all of exon 2, and the 5’9 portion of intron II; clone 3 (4 kb) contains the 3’9 portion of intron II, all of exon 3, and the 5’9 portion of intron III; clone 4 (12 kb) covers the 3’9 portion of intron III, all of exons 4–8 and introns IV–VII, and the 5’9 portion of intron VIII; clone 5 (4 kb) contains the 3’9 portion of intron VIII, all of exon 9, and the 3’-NFR; and clone 6 contains the 5’9 portion of intron I, all of exon 1, and the 5’-NFR.

The Ctpct gene is approximately 26 kb in length, which is ~17 times the length of the CT cDNA. The gene is composed of 9 exons interrupted by 8 introns. Exon 1 contains the 5’-UTR with interruption by intron I at 10 base pairs upstream of the ATG start codon, which is in exon 2; exon 9 contains the 3’-UTR (Figs. 1 and 4). The sizes of the exons range from 72 to 548 bp (Table II), and the sizes of the introns, which were estimated by PCR amplification using a pair of primers located on flanking exons (see Table III), range from 0.5 kb to 6 kb (Fig. 1 and Table III). All exon-intron boundaries were sequenced and are listed in Table III. The boundary sequences at the 5’- and 3’-ends of all of the introns are GT and AG, respectively (Table III), which are consensus sequences for pre-mRNA splicing recognition donor and acceptor sites (14). As described in detail under “Discussion” and depicted in Fig. 1, the organization of the exons of the Ctpct gene are related to the distinct functional domains of the CT enzyme.

**Determination of Transcriptional Initiation Sites and Putative Promoter Region of the Murine Ctpct Gene**—The transcriptional initiation sites of the Ctpct gene were determined by 5’-RACE PCR. PCR was performed using a 5’-fragment of 129/J murine liver CT cDNA tailed with oligo-dC as template; the set of primers used were an abridged anchor primer and primer No. 305 (Table I and Fig. 2A). The reaction generated products of two distinct sizes, 400 and 370 bp, as shown in Fig. 2B. Southern blots of these PCR products hybridized with a 5’-CT cDNA probe (Fig. 2B), indicating that both products were

| Table II Positions and sizes of exons in the 129/J murine Ctpct gene |
| Exon No. | Position in putative 129/J murine cDNA | Codon sequences interrupted | Amino acids at sequence interruption |
| 1 | 1–72 (72) | no codon | untranslated |
| 2 | 73–199 (127) | GTT/GGT | Val39-Gly40 |
| 3 | 200–299 (100) | T/GT | Cys73 |
| 4 | 300–416 (117) | G/TC | Arg112 |
| 5 | 417–568 (152) | CGG/ATT | Gln153 |
| 6 | 569–647 (79) | GC/AG | Gly230 |
| 7 | 648–790 (143) | AAC/GAG | Asn236-Glu237 |
| 8 | 791–979 (189) | CTG/AAG | Leu299-Lys300 |
| 9 | 980–1527 (548) | |

* Number in parentheses equal size of the exon in base pairs.
of the 5′-UTR of CT cDNA and its location on the Ctpct gene.*

Using a computer analysis of the 5′-NFR, a number of potential transcription factor-binding sites were revealed, as indicated in Fig. 3. A total of five potential Sp1 binding sites (GC boxes) (18) were located at positions −9, −58, −66, −70, and −144; the sites at −66 and −70 are overlapping. An AP1 site (ATGAGT-CCAGTGATTAGGTTT) was located at position −350, an AP3 site (GCCGC-GGCC) was located at position −204, and an AP3 site (TGTTGTTCT) at position −107. Two TFIIIA sites (CGGGCTCGAA and CAGTCGCGAA) were located at positions −319 and −381. Two reversed Y1 sites (AGAGGGCGGG and AGCCGGCGGG) were located at positions −73 and −92; the first overlaps with an Sp1 site, and the second overlaps with AP2 and TFIIIA sites.

Determination of the 3′-UTR of CT cDNA and its location on the Ctpct gene—5′-RACE PCR (see “Experimental Procedures” and Fig. 4A) yielded a 370-bp product whose sequence is shown in Fig. 4B. The sequence from the stop codon (TAA) to the terminal adenine, which is the site where polyadenylation occurs, is 341 bp (3′-UTR). Although a 3′-terminal adenine is typical (19), an unusual polyadenylation signal sequence
The structure of the murine Ctpct gene reveals several interesting points. First, the organization of the exons has a distinct relationship to the functional domains of the CT protein (Fig. 1). Exon 2 encodes the first 39 amino acid residues of CT, which includes a signal sequence (residues 8–28) that targets CT to the nucleus (21), where the enzyme is localized in certain cell types (22). Exon 3 encodes residues 40 through 72, for which no specific function has been reported. Exons 4–7 code for the catalytic domain (residues 73–236) (3); exon 4 contains the codons for a HSGH motif (residues 89–92), which is thought to mediate binding of CTP by the enzyme (23). Exon 8 encodes amino acids 237–299, which contain a 58-residue α-helix containing three contiguous 11-residue repeats (residues 256–288); this α-helix is thought to play an important role in the membrane-binding properties and enzymatic activity of CT (5, 24, 25). This exon also encodes a densely positively charged region, a cluster of five lysine residues within a 7-amino acid stretch (residues 248–254), the function of which is unknown. Exon 9 codes for the C-terminal part of the CT protein (residues 300–367), which includes a second α-helix (shown not to be necessary for membrane binding (26)) and multiple serine residues that become phosphorylated in vivo (27, 28); phosphorylation of these serines may interfere with the binding of CT to membranes (29, 30) and with the activation of CT by lipid activators, such as PC/oleic acid liposomes (31). Interestingly, the catalytic domain of mammalian CT is highly homologous to yeast CT while the nuclear localization signal, membrane-binding, and phosphorylation domains of mammalian CT are not (24, 32). Thus, it appears as if the exons encoding the basic catalytic unit of CT evolved first and were later embellished with additional exon cassettes resulting in more complex post-translational regulatory control.

Other interesting features of the murine Ctpct gene include the use of two transcriptional initiation sites, the presence of an untranslated exon 1 that is approximately 6 kb upstream from the initiation codon in exon 2, and the large size of the gene. Other genes involved in lipid biosynthesis, transfer, and metabolism also have an untranslated first exon, including the genes encoding phosphatidylethanolamine transferase-2 (PEMT2) (33), apolipoproteins A-I, A-II, C-II, C-III, and E (34), and phospholipid transfer protein (35). The gene for PEMT2, a 199-amino acid integral membrane protein that catalyzes the synthesis of PC in hepatocytes, has three other features in common with the Ctpct gene, namely two transcriptional initiation sites, a very large size (~30-fold larger than its cDNA versus ~20-fold larger for the Ctpct gene), and the absence of a TATA or CAAT box in the 5′-upstream region of the gene (see below) (33). Whether these similarities denote common transcriptional regulatory features between the two PC biosynthetic genes must await further studies on both genes.

In this regard, the cloning of the Ctpct gene will hopefully lead to future studies directed at understanding how transcription of the CT gene is regulated. The 5′-upstream sequence revealed no TATA or CAAT box, but this region is rich in G + C (71% in the first 350 upstream nucleotides) and contains five GC boxes corresponding to consensus Sp1-binding sites (36) (Fig. 3). Sp1-binding sites have been shown to be present in promoters of numerous viral and cellular genes and generally located at 40–100 nucleotides upstream of the transcriptional initiation sites (36); in the putative Ctpct promoter region, three potential Sp1-binding sites (~58, ~66, and ~71) are present in this region. Lack of a TATA or CAAT box, multiple origins of transcription, and GC-rich Sp1-binding sites are often found together and are typical of housekeeping genes (37–41). Other consensus transcriptional factor-binding sites found in the 5′-upstream region of the Ctpct gene include those for AP1, AP2, AP3, TFIIB, and Y1 (Fig. 3); these sites and those for Sp1 are concentrated in two areas of the putative promoter region, namely between nucleotides ~14 and ~140 and between ~310 and ~392 (Fig. 3). Future studies will determine whether Sp1 and these other factors are involved in basal transcription of the gene or in transcriptional regulation, such as might occur during growth factor stimulation of certain cells (7), after partial hepatectomy in rat liver (9), and after overexpression of PEMT2 in hepatoma cells (8).

The major impetus for our laboratory to clone the Ctpct gene is the ability to study the regulation of the gene and the function of the encoded protein in vitro and in vivo.
was related to our interest in the role of the CT enzyme and PC biosynthesis during atherogenesis (10–12) and our plans to study this relationship in vivo using induced mutant mice. Cloning of the gene was necessary for future gene targeting to create induced mutant mouse models of altered arterial wall PC biosynthesis. Additional induced mutant mouse models using CT constructs mutated in regions thought to be important in post-translational regulation (e.g., phosphorylation or membrane-binding domains) and in the consensus cis-acting sequences of the putative promoter region of the Cptct gene will also be useful in understanding the regulation of CT in vivo.

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