Surfactant protein C (SP-C) is expressed in alveolar Type II epithelial cells of the lung. In order to determine the mechanism(s) that regulate gene transcription, we have analyzed the activation of the murine SP-C promoter in mouse lung epithelial cells (MLE cells) and in HeLa cells after co-transfection with a vector expressing rat thyroid transcription factor-1 (TTF-1). TTF-1 trans-activated SP-C-chloramphenicol acetyltransferase constructs containing –13 kilobase pairs to –320 base pairs (bp) of the 5’ flanking region of the SP-C gene. Essential cis-acting elements were functionally localized to between –320 and –180 bp from the start of transcription by transfection analysis. Five DNase-protected regions, indicating multiple protein-DNA interactions within the –320 bp TTF-1-responsive region of the SP-C gene, were identified by DNase footprint analysis. A 40-bp segment of SP-C DNA from –197 to –158 linked to a heterologous promoter-chloramphenicol acetyltransferase construct activated expression after co-transfection with CMV-TTF-1 in HeLa and MLE cells. The –197 to –158 segment contained two consensus TTF-1 sites, which were specifically identified as TTF-1 binding sites by gel retardation and antibody supershift with MLE cell nuclear extracts and purified TTF-1 homeodomain protein. Site-specific mutagenesis of either of the TTF-1 binding sites completely blocked activation by TTF-1, indicating both sites are required for TTF stimulation of SP-C transcription.

Pulmonary surfactant is a mixture of phospholipids and proteins, which functions to reduce surface tension at the air/liquid interface preventing alveolar collapse during respiration (1). A surfactant deficiency is the basis of lethal respiratory distress syndrome in infants born prematurely. Surfactant protein C (SP-C) is a 3.7-kDa hydrophobic protein that associates with surfactant lipids and is a component of replacement surfactants used in the treatment of neonatal respiratory distress syndrome (2, 3). The alveolus is lined by two morphologically distinct epithelial cell types: the alveolar Type I cells responsible for gas exchange and the cuboidal Type II cells, which contain numerous lamellar inclusion bodies, the intracellular form of surfactant (4). In the adult lung, SP-C is exclusively synthesized and secreted by Type II cells (5–7). In contrast, the other surfactant-associated proteins (SP-A, SP-B, and SP-D) are expressed in both Type II and subsets of airway epithelial cells in the conducting airway (5, 8, 9). SP-C transcriptional activity is detected in primordial respiratory epithelial cells at the earliest stages of lung development (fetal day 11 in the mouse), is restricted to the distal most portions of the developing fetal lung, and is maintained in alveolar Type II epithelial cells in the postnatal lung (6, 7).

As a first step in identifying the cis-active regulatory elements that confer the Type II cell-specific, developmental, and humoral regulation of SP-C gene expression, we have cloned and sequenced both the human and the murine SP-C genes and their flanking sequences (10, 11). In transgenic mice, 3.7 kb of the 5’ flanking sequences of the human SP-C gene is sufficient to produce lung-specific expression of several reporter constructs (11–14). The developmental expression of the 3.7 kb SP-C-CAT transgene mimics the endogenous SP-C gene, indicating that the cis-active regulatory elements essential for both cell-specific and developmental expression are located within 3.7 kb of the transcriptional start site of the human gene (9, 15). Parallel experiments with the murine SP-C promoter (which shows extensive sequence homology to the human promoter) support these same conclusions for 4.8 kb of the murine promoter.2

In the current study we demonstrate the critical role of TTF-1 in the transcriptional regulation of the murine SP-C gene. TTF-1 is a homeodomain containing transcription factor expressed in the developing thyroid, brain, and lung (16). The spatial and temporal pattern of TTF-1 expression in the lung parallels that of SP-C. TTF-1 is detected in the lung rudiments at the earliest stages of epithelial migration into the pulmonary mesenchyme and is maintained in epithelial cells of the distal conducting airways and alveoli (16, 17). SP-C expression appears only slightly later on murine fetal day 11, but is restricted only to alveolar expression with further development. Two recent studies demonstrate that TTF-1 activates the transcription of surfactant proteins A and B (18, 19). Here we extend those observations to SP-C and identify specific cis-acting sequences involved in transcriptional regulation of the SP-C promoter by TTF-1.

MATERIALS AND METHODS

Plasmid Constructions and Site-directed Mutagenesis—Large portions of the murine SP-C promoter sequences were retrieved from a murine 129/J genomic library (gift of Roger Ashken, University of Cincinnati) using human SP-C cDNA sequences as probes (11). A 5-kb XbaI fragment was subcloned and subject to Bal31 digestion from a unique KpnI site to remove the first intron and the coding portion of the first exon, blunt end-ligated to XhoI linkers, and directionally cloned into the

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2 S. E. Kelly and S. W. Glasser, unpublished observations.
promoterless plasmid pBLCAT6 (20) using the Accl and XhoI sites. Sequencing determined that this test construct (p4.8 muCAT) contains 4.8 kb of murine promoter sequence and 18 bp of the first exon, followed by the introduced XhoI site and then the vector-derived reporter gene, chloramphenicol acetyltransferase (CAT). Deletions of p4.8muCAT were produced with restriction sites that cut uniquely in the murine

![Deletional analysis of the SP-C promoter.](image)

**A**, a representative autoradiogram shows the TLC separation of acetylated chloramphenicol products (dark arrowheads) from unreacted substrate (light arrowhead) catalyzed by extracts from MLE-15 cells transiently cotransfected (duplicate plates) with the p4.8 muCAT test construct and pCMV-TTF-1, pCMV-HNF-3x, or pCMV-HFH-8. The transactivators are expressed under the control of the CMV promoter, and the control assays are transfections with pRCMV, the empty vector. The extracts were normalized for transfection efficiency as determined by β-galactosidase activity.

**B**, a representative autoradiogram shows the TLC separation of acetylated chloramphenicol products from unreacted substrate as catalyzed by extracts from MLE-15 cells transiently transfected with the deletion constructs. The length of the murine SP-C promoter is indicated (in kilobases) beneath the autoradiogram. The plus signs indicate cotransfection with recombinant rat TTF-1 (from plasmid pCMV-TTF-1), and the minus signs indicate cotransfection with the empty vector pRCMV. pBLCAT6 is the promoterless reporter vector; pBLCAT5 has the reporter gene under the control of the HSV-TK promoter. The extracts were normalized to transfection efficiency as determined by β-galactosidase activity.

**C**, the relative CAT activity of MLE-15 cells transiently transfected with the indicated deletion test constructs. The CAT activity is expressed relative to pBLCAT6, the promoterless plasmid, with black bars representing CAT activity in the presence of coexpressed TTF-1 (from plasmid pCMV-TTF-1) and white bars in its absence (cotransfected with pRCMV). The plasmid pBLCAT5 has the constitutive HSV-TK promoter, which is unresponsive to TTF-1. The bars each represent a mean relative CAT activity from at least three independent transfections each done in duplicate. Shown at left of the graph are diagrammatic representations of the test constructs, identified by the length in kilobases of the SP-C 5' flanking sequences (thick line) and showing the SP-C transcriptional start site with +1 and an arrow.

**D**, shown is the relative CAT activity of HeLa cells transiently transfected with the indicated deletion test constructs in the presence (dark stippled bars) and absence (light stippled bars) of TTF-1.
promoter and in the multiple cloning region of pBLCAT6 (Spfl for the 0.8-kb construct and PstI for the p0.32mcuCAT) or the blunt PstI site of the multiple cloning region of pBLCAT6 and EcoN1 for 0.23-kb, partial DraII for 0.18-kb, and BstXI for 0.10-kb constructs.

To produce herpes virus-thymidine kinase (HSV-TK) promoter constructs, fragments of the murine SP-C 5' flanking regions were blunt ended and inserted into the BamHI site distal to the HSV-TK promoter of pBLCAT5 (20). The orientation and oligomerization of the inserts were determined by sequencing.

For site-directed mutagenesis of potential TTF-1 sites T4 and T5, the SP-C promoter region was liberated with PstI and XhoI from p0.32mcuCAT. This 320-bp fragment was subcloned into the pG2L8 basic (Promega) vector producing pSP-C wt. Site-specific mutations in the SP-C promoter were created by two separate PCR reactions using either the sense or anti sense mT4 or mT5 oligonucleotide and the corresponding vector oligonucleotides (GL1 or GL2, Promega) to generate PCR products that overlap at the site of mutation. A second PCR reaction using the vector oligonucleotide primers and the products of the first PCR reaction generated the mutant 320-bp SP-C promoters. The presence of the expected mutations was verified by sequencing.

Transfection and Reporter Gene Assays—Functional assays of reporter constructs were performed using transient transfection by the calcium phosphate co-precipitation method of MLE-15 cells and HeLa cells (21). MLE-15 is an SV40 large T-antigen immortalized mouse lung epithelial cell line that maintains morphological and functional characteristics of pulmonary Type II epithelial cells (22). Cells in 60-mm dishes at 40–50% confluence were transfected with three plasmids at the following concentrations: 1.67 pmol of test construct, 0.33 pmol of vector oligonucleotide primers and the products of the first PCR reaction that overlap at the site of mutation. A second PCR reaction using the vector oligonucleotide primers and the products of the first PCR reaction generated the mutant 320-bp SP-C promoters. The presence of the expected mutations was verified by sequencing.

Nuclear Extract Preparation—Nuclear extracts were prepared using a mini extract procedure (23) as modified by Bohinski et al. (19). Nuclear extract protein concentrations were determined by a bicinchoninic acid assay (Pierce) using bovine serum albumin as a standard.

Electrophoretic Mobility Shift Assays—Electrophoretic mobility shift assays were performed essentially as described (19). Briefly, 5–10 μg of nuclear extract was incubated in buffer C (12 mM HEPES, pH 7.9, 25 mM KCl, 5 mM MgCl2, 1 mM EDTA, 50 μg/ml poly(dI-dC) (Boehringer Mannheim), 10% glycerol, 1 mM dithiothreitol, 0.5 mM fresh phenylmethylsulfonil fluoride), and when indicated, with unlabeled competitor DNA for 5–10 min on ice. Labeled probe was added (100,000 dpm), and the mixture was incubated for 10 min on ice. For antibody supershift-interference assays, 1 μl of purified anti-TTF-1 antibody was added and the incubation was continued for an additional 20 min. Nuclear extracts were resolved on 6% polyacrylamide, 7 M urea sequencing gels using 320 bp XhoI and PstI for the 0.10-kb constructs. Fragments of the murine SP-C 5’ promoter were created by two separate PCR reactions using either the sense or anti sense mT4 oligonucleotide and the corresponding vector oligonucleotide (GL1 or GL2, Promega) to generate PCR products overlapping at the site of mutation. A second PCR reaction using the vector oligonucleotide primers and the products of the first PCR reaction generated the mutant 320-bp SP-C promoters. The presence of the expected mutations was verified by sequencing.

RESULTS

The SP-C Promoter Is Transactivated by TTF-1—In order to determine whether SP-C promoter sequences were responsive to activation by transcription factors that stimulate genes expressed in airway epithelial cells, MLE-15 cells were cotransfected with a 4.8-kb SP-C-CAT construct and a second plasmid that constitutively expressed one of the recombinant transcription factors TTF-1, HNF-3α, or HFH-8. CAT assays of cell extracts demonstrated that the SP-C promoter was transactivated by coexpression of TTF-1 but was not transactivated by HNF-3α (which activates SP-B expression) or HFH-8 (which has been localized to the distal pulmonary parenchyma) (24) (Fig. 1A).
Seven SP-C-CAT deletion constructs containing sequences from 13 to 0.10 kb of murine SP-C promoter were used to map regions essential for SP-C transcriptional activity and to localize the TTF-1-responsive region. Plasmids containing from 13 to 0.32 kb of 5' SP-C flanking sequence were approximately 10-fold more active than the promoterless CAT reporter plasmid in transient transfections of MLE-15 cells (Fig. 1B). Deletion of SP-C promoter sequences from 0.32 to 0.23 kb reduced basal activity to only 4-fold over background, identifying a potential stimulatory element located between 0.32 and 0.23 kb. TTF-1 stimulated CAT activity approximately 7-fold in constructs containing 4.8 or 0.8 kb of SP-C DNA and 10-fold in the test constructs with 0.32 kb of 5' flanking sequences fused to the HSV-TK promoter (Fig. 1C). Further deletions resulted in two discrete reductions in TTF-1-mediated transactivation. The level of TTF-1 stimulation was reduced to 2–3-fold with the 0.23 SP-C-CAT construct and all TTF-1 response was lost in cotransfection with the 0.18 SP-C-CAT construct. These results functionally map the location of TTF-1 transcriptional control elements necessary for SP-C transcription to positions 200 to 180.
transactivated SP-C-CAT constructs in the HeLa epithelial cell line (Fig. 1D), while the same SP-C-CAT constructs were inactive in the 3T3 fibroblast cell line (data not shown).

Footprint Analysis of the −320 SP-C Region Identifies Multiple Sites of Protein-DNA Interactions—The 0.32-kb promoter proximal region identified by deletion analysis as sufficient for maximal transactivation by TTF-1 was analyzed to determine the specific sites of DNA-protein interactions. Five distinct regions were protected from in vitro DNase I digestion by nuclear extracts from MLE-15 cells as compared to nuclear extracts from 3T3 cells or control reactions containing only equivalent amounts of the nonspecific protein BSA (Fig. 2).

Footprint region C1 (approximately −78/-117) was present in both 3T3 and MLE-15 nuclear extracts and overlaps the truncated 0.10-kb construct that was transcriptionally inactive in transfection assays (Fig. 1). Footprint C2 (−167/-186) was clearly defined in the lung cell-derived MLE-15 nuclear extract but was not protected by the 3T3 nuclear extract. The C2 (−167/-186) region was disrupted in the 0.18-kb deletion construct but, along with C3 (−200/-222), was retained in the TTF-1-responsive 0.23-kb construct. Footprint C3 was detected in both extracts, but shows differences in the 5' boundary of the footprint. A DNase I hypersensitive site was found with both nuclear extracts at −214 within this region. Footprint C4 (−278/-291) was protected over a larger region by MLE-15 extracts than by 3T3 extracts and was separated from footprint C5 (−295/-309) by only three unprotected bases. Thus, this region of the murine SP-C promoter (−309/-78) contains at least five distinct DNA-protein interactions.

Figure 4. Point mutations identify specific sequences necessary for TTF-1 binding. A, sequences of the probes and competitors used in the electrophoretic mobility shift assays. C2 is the 24-bp double-stranded probe corresponding to the wild type murine SP-C sequence (−186/-163) encompassing the minimal TTF-1 motifs numbers 4 and 5 (underlined). mT4 and mT5 are mutant versions of the SP-C probe with the indicated mutations (in bold letters) in motifs 4 and 5, respectively. SP-B is a 24-bp double-stranded oligonucleotide from the human SP-B promoter (−313/-90), which had been identified as binding TTF-1, and mSP-B is the multiple mutant version of the same. Putative TTF-1 consensus sequences are underlined in all cases. B–D, shown are autoradiograms of electrophoretic mobility shifts of SP-C probes containing the number 4 and 5 minimal TTF-1 motifs. Open arrows indicate the position of the free probe; closed arrows indicate the specific protein-DNA complexes. B, wild type SP-C probe (C2) is complexed with MLE-15 extracts and competed with 100-fold excess of unlabeled self (C2), and mutant (mT4 and mT5) oligonucleotides. C, wild type SP-C probe (C2) is complexed with MLE-15 extracts and competed with unlabeled self (C2), human SP-B (SPB), and mutant human SP-B (mSPB) oligonucleotides. The asterisk indicates the addition of TTF-1-specific antibodies. The stippled arrowhead indicates the position of the supershifted complex. D, wild type (C2) SP-C probe forms a specific complex with purified recombinant TTF-1 homedomain protein (TTF-1 HD). Mutant oligonucleotides display minimal (MT4) or no binding (MT5) to the truncated TTF-1 homedomain peptide.

region, a region containing only the T4–T6 consensus elements.

TTF-1 Protein Binds to Sequences of the SP-C Promoter—The TTF-1-responsive consensus elements T4 and T5 located within the footprint C2 were tested for their ability to form specific protein-DNA interactions with nuclear extracts from MLE-15 cells (Fig. 4). A single, strong shifted band corresponds to a protein-DNA complex that forms on the wild type SP-C probe (C2: −186/-163). Specificity of these interactions was shown by competition with unlabeled probe as well as an oligonucleotide from the promoter proximal TTF-1 binding site of the SP-B promoter (19). Separate mutations of either the T4 or T5 consensus elements in the C2 oligonucleotide (mT4 or mT5) prevented competition of complex formation with the wild type C2 oligonucleotide, demonstrating that both T4 and T5 were required for specific TTF-1-protein DNA binding. The sequence of these oligonucleotides are shown in Fig. 4A and electrophoretic mobility shifts in Fig. 4 (B–D). The protein-DNA com-
plex formed from MLE-15 nuclear extracts was supershifted by TTF-1-specific antisera (Fig. 4C). Recombinant rat TTF-1 homodomain also bound specifically to the SP-C oligonucleotide C2 probe, producing a single shifted complex (Fig. 4D). Oligonucleotide mt4 retained residual binding to TTF-1 homodomain when compared to mt5 (Fig. 4D) and showed partial competition for complex formation with the wild-type C2 probe (Fig. 4B).

Site-specific Mutagenesis of the TTF-1 Element Eliminates Transactivation—Mutation of binding site T4 or T5 in the context of the 0.32 SP-C promoter fragment was used to assess the relative importance of each binding site for TTF-1 transactivation. A mutation in either CAAG element (SPCmT4 and SPCmT5) abolished the transactivation by TTF-1 as compared to the wild type 0.32 SP-C LUC (SP-C wt) in MLE-15 and HeLa cell lines (Fig. 5), demonstrating that both T4 and T5 minimal TTF-1 motifs are required for TTF-1 transactivation.

**DISCUSSION**

In this report we demonstrate that the homeodomain transcription factor TTF-1 binds to and activates the murine SP-C promoter. Cotransfection of plasmids producing TTF-1 with SP-C-CAT reporter constructs delineated a minimal region of the SP-C gene that was sufficient to activate transcription in MLE-15 and HeLa cells. This region of the SP-C gene contained two sites (within nucleotides -2186 to -2163) that bound TTF-1 or recombinant TTF-1 homeodomain in vitro. Mutation of either TTF-1 motif interfered with TTF-1 binding and eliminated the ability of TTF-1 to activate transcription, demonstrating that both TTF-1 binding sites were required for the activation of the SP-C promoter.

TTF-1 expression is limited to the thyroid, brain, and lung in the adult rat and human (16). TTF-1 transactivates the thyroglobulin, thyroperoxidase, and thyrotropin receptor genes in thyroid carcinoma cell lines and binds to a consensus 5'-
CAAG-3 motif distinct from other homeobox genes (25, 26). TTF-1 was recently identified as a transactivator of genes encoding surfactant proteins as well as a Clara cell-specific gene (18, 19). In the lung, TTF-1 mRNA temporally precedes SP-C expression, and, like SP-C, is restricted to epithelial cells at the distal tips of developing airway during branching morphogenesis. These observations support the hypothesis that TTF-1 may be a critical determinant of SP-C gene transcription.

Our analyses of the SP-C promoter and adjacent sequences have shown that the TTF-1-responsive region of the murine SP-C promoter contains two functional CAAG elements configured on opposite strands of DNA as part of a 13-bp palindrome at nucleotides -182 to -170. Analysis of other TTF-1-activated genes demonstrates that transcriptional stimulation is achieved by action at multiple TTF-1 binding sites and suggests this as a mechanism for differential expression of genes by TTF-1 (27). The similarities and differences in the arrangement and context of defined binding sites in TTF-1-responsive promoter regions from both thyroid- and lung-specific genes are summarized in Fig. 6. The TTF-1 binding site in the SP-C promoter is similar to the composite TTF-1-responsive region of the rat thyroglobulin gene where two core CAAG elements are arranged with dyad symmetry. An array of four TTF-1 binding sites was identified in the murine SP-A promoter clustered over the -166 to -117 region (18). Electrophoretic mobility shift assay experiments with SP-A binding site probes identified differential binding affinities for TTF-1 (18). SP-B has two distinct TTF-1 binding sites, both of which are required for transactivation by TTF-1 (19), consistent with our findings for TTF-1 stimulation of SP-C transcription. The two essential TTF-1 binding sites identified adjacent to the SP-B promoter are notable in their degenerate recognition site. Thus the configuration (linear, palindromic), number, and sequence of TTF-1 binding sites are arranged in a distinct profile for each gene. In the sequence comparison of Fig. 6, we highlight a common sequence motif consisting of (G/A)(G/T)GCCT, which is closely apposed to the core CAAG motifs of the thyroid- and lung-specific TTF-1-responsive genes. This region warrants further investigation because mutations that have altered this sequence (in conjunction with mutations in TTF-1 response elements) have dramatically reduced expression of reporter constructs (19, 27, 28).

Cooperative binding of homeodomain protein to clustered DNA binding sites has been reported for several diverse homeodomain transcription factors (29, 30) similar to the tandem binding sites found in the SP-C promoter and the other TTF-1-responsive genes. The requirement for cooperative TTF-1 binding to establish activation is supported by the consistent observation that mutation of one binding site eliminates TTF-1 transactivation. Cooperative binding may serve to stabilize transcription complexes or produce a tight regulation of the target gene due to concentration of TTF needed to fully occupy multiple sites. In addition to the unique array of composite TTF-1 binding sites for each gene, varying cellular concentrations and distinct intracelluar forms of TTF-1 could account for differential regulation of surfactant protein genes by TTF-1.

TTF-1 is uniformly expressed at high levels in distal epithelial cells of the branching airway during lung development (16, 17). In the postnatal lung, TTF-1 was detected most abundantly in alveolar Type II cells and at reduced levels in subsets of differentiated bronchial epithelial cells (17). TTF-1 was undetectable in Type I cells. This distribution of TTF-1 is consistent with the developmental profile and cells of the mature lung that differentially express SP-A, -B, and -C genes. TTF-1 has recently been shown to undergo sulfhydryl-dependent oligomer formation, which affects its binding properties for clustered cis-active sites (31). These experiments suggest that within a cell, monomeric and higher order toxins of TTF-1 may exist that could alter the binding and stability of TTF-1 DNA complexes. Thus, the different configurations of TTF-1 binding sites in conjunction with varied TTF-1 concentrations and oligomeric forms of TTF-1 in a cell could produce the heterogeneity of SP-A, -B, and -C expression in specific distal epithelial cells.

Factors other than the abundance of TTF-1 must further distinguish thyroid from lung cell expression and specify Type II cell expression of SP-C. Transcriptional control of TTF-1-regulated genes appear to operate by distinct mechanisms in thyroid and lung. The transcription factors HNF-3α and TTF-1 bind to adjacent sites in the SP-B promoter and are synergistic in stimulating transcription (19). This is distinct from the mechanisms operating in the thyroid where the paired box factor, PAX-8, and TTF-1 utilize overlapping recognition sites and bind in a mutually exclusive manner to composite sites (32). Binding of either PAX-8 or TTF-1 is sufficient to transactivate thyroglobulin promoter constructs in thyroid cells or in HeLa cells. The footprint analysis of the SP-C promoter suggests that additional sites for protein-DNA interaction flank the TTF-1 binding sites. The nature and number of these binding factors is unknown, but we speculate that their combinatorial binding may alter accessibility and the dynamics of TTF-1 activation. The present work supports a model where TTF-1 plays a critical role in the transcriptional regulation of the SP-C gene in Type II cells by interacting with two adjacent cis-active elements (917 to 158), with cell selective expression of SP-C modulated by an enhancer element located in the -320 to -230 region. These unique combinations of TTF-1 with other factors specific to thyroid or lung as well as distinct binding affinities of the sites for TTF-1 may contribute to cell-selective and organ-specific expression of TTF-1 responsive genes in the lung and thyroid.

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Transcription of the Lung-specific Surfactant Protein C Gene Is Mediated by Thyroid Transcription Factor 1

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