Surfactant protein B (SP-B) is selectively expressed in bronchiolar and alveolar epithelial cells of the lung. We identified an upstream enhancer located in the 5'-flanking region of the human SP-B gene (−439 to −331 base pair, hSP-B(−439/−331)) by deletion analysis of SP-B-luciferase constructs assessed in transfection assays in vitro. The element cis-activated the expression of an SV40 promoter-luciferase reporter gene in a human pulmonary adenocarcinoma cell line (H441-4). Three distinct binding sites for the nuclear transcription protein, thyroid transcription factor 1 (TTF-1), were identified, and the purified TTF-1 homeodomain was bound to the region of hSP-B(−439/−331). Co-transfection of H441-4 cells with the expression vector pCMV-TTF-1 trans-activated the native human SP-B promoter and the SV40 promoter fused with the SP-B enhancer. Mutations of the TTF-1 binding sites in the upstream enhancer blocked TTF-1 binding and transactivation activity. In summary, TTF-1 interacts with distinct proximal (−80 to −110) and distal (−439 to −331) cis-acting elements that regulate lung epithelial cell-specific transcription of the human SP-B gene.

Surfactant protein B is a small, hydrophobic protein that interacts with phospholipids to reduce surface tension at the air-liquid interface of the alveoli in the lung. Deficiency of SP-B is associated with lethal neonatal respiratory failure in humans (1) and in transgenic mice in which the SP-B gene was deleted by homologous recombination (2). Immunohistochemically, in situ hybridization and the promoter analysis indicated that surfactant protein B is expressed in a lung epithelial cell-specific manner (3). The lung epithelial cell specificity of surfactant protein gene expression is mediated at the level of gene transcription (4). Analysis of the 5′ regions of several genes expressed in a lung-specific manner (SP-A, -B, -C, and Clara cell secretory protein) supports an important role for transcription protein activating this SP-B enhancer element in the trancriptional initiation site. The hSP-B (−439/−331) element activated an upstream enhancer activity in the 5′-flanking region of the human SP-B gene located at −439 to −331 nucleotides upstream of the transcriptional initiation site. The TTF-1 −439/−331 element activates the SV40 promoter activity in forward and reverse orientations in H441-4 cells. Mobility shift assay, point mutation, and transfection assays showed that TTF-1 is the critical nuclear transcription protein activating this SP-B enhancer element in the human gene.

MATERIALS AND METHODS

Plasmid Constructions and PCR-mediated Site-directed Mutagenesis—The human SP-B promoters with various lengths and regions were generated by polymerase chain reaction (PCR) using Taq DNA polymerase (Life Technologies, Inc.), synthetic oligonucleotide primers, and the pRSV-650 SP-B CAT construct as a template (10). The upstream primer with the MuI site for the B-281 construct is 5′-CGACACGCGTCGACATGGGTTGTA-3′. The upstream primer with the MuI site for the B-500 construct is 5′-CGACACGGTCACAGGAAAGATTTCACAGGGGAA-3′. The downstream primer with the XhoI and MluI sites for the B-281 and the B-500 construct is 5′-CGGTCGAGCCCTGCTGCTGCTGCTTC-3′. The downstream primer with the XhoI site for the B-281 and the B-500 construct is 5′-CGGTCGAGCCCTGCTGCTGCTGCTTC-3′. The downstream primer with the XhoI site for the SV40-P-F construct is 5′-CGACACGGTCAGGGCTGCTGCTGCTTGTAAG-3′. The downstream primer with the XhoI site for the SV40-P-F construct is 5′-CGGTCGAGCCCTGCTGCTGCTGCTTC-3′. The upstream primer with the MuI site for the SV40-P-R is 5′-CGACACGGTCACAGGAAAGATTTCACAGGGGAA-3′. The downstream primer with the XhoI site for the SV40-R construct is 5′-CGGTCGAGCCCTGCTGCTGCTGCTTC-3′. The PCR products were digested with MluI and XhoI restriction enzymes (Life Technologies, Inc.) and ligated with MluI/XhoI-digested pGL2-B or pGL2-P luciferase reporter plasmids (Promega). The oligonucleotide sequences for the PCR II-C are upstream primer 5′-CAGGCGCTCTGCCTGCTCTTAA-3′ and downstream primer 5′-GCCGAGGCTCTGCCTCACC-3′. The PCR product was directly subcloned into the PCR II vector as described by the manufacturer (Invitrogen).
To generate the site-specific mutants of B-500 construct at the TTF-1 binding sites, two steps of PCR were conducted. For the first PCR, proper mutant PCR oligonucleotides were synthesized with mutations at the position indicated in Fig. 6A. The mutant primers were mixed with the pGGL-2B vector primer GLprimer 1 and GLprimer 2 to make two sets of PCR products that were subsequently purified by low melting point agarose gel electrophoresis and the QIAquick gel extraction kit. The purified PCR products were then mixed together along with GLprimer 1 and GLprimer 2 primers for the second PCR. The second PCR products were digested with MluI/Xhol restriction enzymes for 3 h at the 37° C. The DNA fragments (553 bp) with MluI- and Xhol-flanking sites at each end were purified by low melting point gel electrophoresis as described above and ligated into the MluI/Xhol-digested pGGL-2B plasmid to generate B-500 Bm8, B-500 Bm6, and B-500 Bm4 mutant luciferase constructs. The correctness of all the wild type and mutant plasmid constructs were confirmed by DNA sequencing.

Cell Culture, Transfection, and Reporter Gene Assays—H441-4 cells were maintained in RPMI medium supplemented with 2 mM glutamine and 10% fetal calf serum (Life Technologies, Inc.). One day before transfection, 5 × 10^5 cells were seeded into 60-mm dishes. Each dish was transfected with 12.5 μg of total plasmid DNA using the calcium phosphate precipitation method and incubated in Dulbecco’s modified Eagle’s medium overnight. The next day, the media were changed to RPMI, and the cells were incubated for 2 days prior to assay. Cell lysis and luciferase assays were performed using the luciferase assay system purchased from Promega. The light units were assayed by luminometry (monolight 1010, Analytical Luminescence Laboratory, San Diego, California). Transfection efficiency was normalized to β-galactosidase activity. Multiple transfections (n = 2–8) were carried out for each experiment, and the mean values were used for data presentation. Standard deviations were generally less than 20%. Plasmids pCMV-Rc (Invitrogen) and pCMV-TTF-1 were kind gifts from Dr. R. Di Lauro, Stazione Biologica, Naples, Italy.

Nuclear Extracts and EMSA—H441-4 cells were grown on 75-mm flasks. Before harvesting, cells were washed twice in Hanks’ solution. The cell pellet was then resuspended in 5 volumes of lysis buffer (50 mM Tris-Cl, 100 mM NaCl, 5 mM MgCl2, and 0.5% (v/v) Nonidet P-40) for 5 min on ice. After centrifugation, the supernatant was saved as cytoplasmic protein extract. The nuclear pellet was resuspended in a 100 μl of nuclear buffer (0.5 mM KCl, 20 mM Tris-Cl, pH 7.6, 0.2 mM EDTA, 1.5 mM MgCl2, 25% glycerol, and 1 mM diithiothreitol) and incubated on ice for 30 min. The resulting DNA pellet was spun down, and the supernatant was used as nuclear extract. Protein extract (5 μg) was used for EMSA as described previously (11). Recombinant rat TTF-1 homodimer (HD) was a kind gift from Dr. Di Lauro. The probes for EMSA were made from either the synthetic oligonucleotides or the PCR product (hSP-B (439–331) fragment).

**Results**

Expression of SP-B, SV40, and Thymidine Kinase Promoters in H441-4 Cells—The −218 to +41 bp (minimal promoter) and the −500 to +41 bp regions of the human SP-B gene were subcloned into the pGGL-2B luciferase reporter gene producing constructs B-218 and B-500 (Fig. 2B). When the B-218 and B-500 promoters were compared with the SV40 and thymidine kinase promoters in H441-4 cells using transient transfection assays, both B-218 and B-500 constructs were more active than the SV40 and thymidine kinase promoters (Fig. 1). Activity of B-500 was 3-4-fold greater than B-218, indicating a potential enhancer element located in the distal upstream region.

Transcriptional Activity and DNA Protein Binding of hSP-B (−439 to −331)—Nucleotide sequence in the 5′-flanking distal upstream regions of the human and mouse SP-B genes share 95% identity from −439 to −331 bp (human) and −382 to −282 bp (mouse). The deletion of this region in mouse SP-B gene dramatically reduced the transcriptional activity (50-fold reduction) as assayed by transient transfection of the mouse lung epithelial (MLE-15) cell line using the chloramphenicol acetyltransferase reporter gene. In order to determine the biological function of the stimulatory element in the human gene, the hSP-B (−439–331) sequence was subcloned into the PCR II

![Fig. 1. SP-B promoter activity in H441-4 cells. Plasmid DNA (12.5 μg/60-mm dish) was used to transfect H441-4 cells. Cells were transfected with 5 μg of pCMV-Rcgal and 7.5 μg of construct B, SV40-P, thymidine kinase (a pGL2-B luciferase reporter construct containing the minimal thymidine kinase promoter), B-218, and B-500. Luciferase assays were carried out in duplicate 2 days after transfection.](http://www.jbc.org/)

J. A. Whitsett, C. Yan, and Z. Sever, unpublished observations.
Fig. 2. A, nucleotide sequence of hSP-B(-439/-331) of the human SP-B gene. The underlined nucleotide consensus sequences (CAAG) are the putative TTF-1 binding sites. Bars (Ba, Bb, and Bc) represent the regions used to design the oligonucleotides for mutagenesis study (see details in Fig. 5). B, plasmid constructs used in transfection assays. a, promoterless pGL2-B luciferase reporter vector (B); b, pGL2-B vector containing the human SP-B promoter region from -218 to +41 bp (B-218); c, pGL2-B vector containing the human SP-B promoter region from 500 to 141 bp (B-500); d, pGL2-B vector containing the SV40 promoter (SV40-P); e, SV40-P vector fused with hSP-B (-439 to -331), the enhancer is forward orientated (SV40-P F); f, SV40-P vector fused with hSP-B (-439 to -331), the enhancer is in reverse orientation (SV40-P R); g, PCP II-C vector containing the hSP-B (-439 to -331) fragment from -218 to +41 bp at the EcoRI site (PCP II-C).

Fig. 3. hSP-B(-439/-331) inhibits hSP-B (-500 to +41 bp) promoter activity in H441-4 cells. Total plasmid DNA of 12.5 μg/60-mm dish was used in transfection, which contains 2.5 μg pCMV-bgal, 1.5 μg of construct B, and 8.5 μg of PCR II (lane B); 1.5 μg of B-218 and 8.5 μg of PCR II (lane B-218); 1.5 μg of B-500 and 8.5 μg of PCR II (lane B-500); or 1.5 μg of B-500 and 8.5 μg of PCR II-C (lane B-500 + PCR II-C). PCR II (Invitrogen) is the parent plasmid of PCR II-C, which contains no hSP-B(-439/-331) insert. Values are mean ± S.D. (n = 4).

the proximal (F₁) element located -111 to -73 bp. The hSP-B(-439/-331) fragment was therefore isolated and ligated to an SV40 promoter-luciferase construct in the forward and re-

Fig. 4. A, TTF-1 binds to the hSP-B(-439/-331) enhancer fragment. Radiolabeled hSP-B(-439/-331) enhancer probe (35,000 dpm) was incubated with 2 μg of H441-4 cytoplasmic (C) or nuclear (N) extracts in the presence of no competitor (-), self-competitor (S), or F₁ fragment (f₁) (containing known TTF-1 binding sites of the human SP-B gene) and run on a 4% polyacrylamide gel. The DNA-binding protein (BP) complex was inhibited by self-competitor or F₁ DNA competitors. B, DNA binding study of TTF-1 HD to the hSP-B(-439/-331) enhancer fragment. Radiolabeled hSP-B(-439/-331) enhancer probe (40,000 dpm) was incubated with 3 ng of purified recombinant TTF-1 homeodomain protein in the presence of no competitor (-), self-competitor (S), F₁ fragment (f₁), or the F₂ fragment (f₂) (containing an HNF-3 binding site) of the human SP-B gene and separated on 4% polyacrylamide gel.
verse orientation producing SV40-P F and SV40-P R (Fig. 2B). The hSP-B(2439/2331) fragment stimulated the SV40 promoter transcriptional activity in both orientations. SV40-P R was more active than SV40-P F (Fig. 5B). Co-transfection of H441-4 cells with pCMV-TTF-1 increased SV40-P F activity 9-fold and SV40-P R activity 19-fold (Fig. 5B).

Mutations in the hSP-B(2439/2331) abolished or reduced the TTF-1 Response—To further confirm that the putative TTF-1 binding to the sites in the hSP-B(2439/2331) fragment mediated transactivation, three wild type TTF-1 sites and three mutant oligonucleotides were synthesized (Fig. 6A), radiolabeled, and incubated with recombinant TTF-1 HD protein and separated by EMSA. Although all three wild type oligonucleotides were shifted by TTF-1 HD, the mobility of mutant oligonucleotides was not altered (Fig. 6B). TTF-1 HD binding to the wild type oligonucleotides was inhibited by 100-fold molar excess of self-competitor. The mutants lacking binding to
TTF-1 HD was introduced into the B-500 luciferase expressing construct. Wild type and mutant B-500 constructs mutated at the positions Bαm, Bβn, and Bεm were transfected into H441-4 cells. As illustrated in Fig. 6C, site-specific mutations in the B-500 constructs decreased transcriptional activity. Mutations at positions Bαm and Bβn reduced transcription to the level of the minimal promoter (B-218) and completely abolished the stimulatory response produced by co-transfection with pCMV-TTF-1. Mutation at the position Bεm only moderately impaired activity. Transcription from the hSP-B (--439−331) fragment was therefore highly dependent on TTF-1 binding to the region.

**DISCUSSION**

Surfactant deficiency in premature infants causes respiratory distress syndrome (1). SP-B plays an important role in maintaining the alveolar stability by enhancing the rate of spreading and the stability of phospholipid at the air-water interface. SP-B exerts important effects on phospholipid structures, contributing to tubular myelin formation, and enhances phospholipid uptake by Type II epithelial cells (3). Genetic ablation of the SP-B gene in transgenic mice caused perinatal respiratory failure associated with atelectasis and the lack of lamellar bodies and tubular myelin in the lungs of newborn SP-B deficient mice (2). Precise regulation of SP-B expression is therefore likely critical to surfactant homeostasis and is mediated, at least in part, by transcriptional mechanisms.

In the present work, an upstream enhancer sequence was identified in the 5'-flanking region of hSP-B (--439−331). This distal element is active in the context of the proximal SP-B promoter-enhancer region and also stimulates transcription from a minimal SV40 promoter construct regardless of the orientation. TTF-1 binds to and activates the enhancer at three distinct sites located within the region --439 to --331 of the human SP-B gene. This conclusion is based on several observations: 1) TTF-1 HD binds to the enhancer sequence and forms multiple distinct complexes; 2) nuclear proteins bind to the upstream SP-B enhancer sequence and were competed by a known TTF-1 binding sequence (F1) and supershifted by the TTF-1 antibody; 3) pCMV-TTF-1 expression vector stimulated the SP-B and the SV40 promoters linked to the upstream SP-B enhancer sequence; 4) mutations at the three putative TTF-1 binding sites on the hSP-B (--439−331) fragment reduced or abolished TTF-1 HD binding transcriptional activity. Dr. Di Lauro and co-workers recently demonstrated that TTF-1 forms intermolecular protein oligomers through its cysteine residues (13), likely accounting for the heterogeneity of the --439 to --331 region of the SP-B gene.

There is increasing evidence supporting the role of TTF-1 in lung development and lung-specific gene expression. The amino acid sequence of TTF-1 has been strongly conserved among mammalian species, canine, rat, and human TTF-1 sharing up to 98% identity (9). In the lung, the distribution of TTF-1 expression is consistent with its role in modulation of surfactant protein expression. Immunohistochemistry and in situ hybridization analysis showed that TTF-1 protein and mRNA were present in a subset of nonciliated bronchiolar epithelial cells in the conducting airways and in the Type II epithelial cells in alveoli. TTF-1 was excluded from the ciliated respiratory epithelial cell and from terminally differentiated Type I epithelial cells in human and rat (9), cells that do not express the surfactant proteins.

The present work demonstrates that homeodomain-containing TTF-1 transcription factor binds complex cis-acting elements in an enhancer located --439 to --331 bp from the start of transcription of the human SP-B gene. These findings, as well as those derived from the analysis of SP-A gene (14), demonstrate that several TTF-1 proteins bind to closely clustered TTF-1 binding sites. Disruption of individual TTF-1 binding sites in each "unit" of the SP-B promoter either abolished or severely impaired the regulatory activity of the element. As shown in Fig. 7, there are at least two such units in the human SP-B gene. Region I consists of two TTF-1 and one HNF-3 binding sites and is located between --111 and --73 bp in the hSP-B gene. Region II consists of three TTF-1 binding sites, located in the --439 to --331 region 5' to the transcriptional start site. The TTF-1 dimer sites were also identified in the SP-A, Clara cell secretory protein, and SP-C promoter and enhancer regions. Table I summarizes the TTF-1 binding sites in the lung gene promoters and enhancers. All of the TTF-1 binding sites have been confirmed to have biochemical or biological functions by DNA footprinting, EMSA, or mutagenesis.

**FIG. 7. Schematic illustration of TTF-1 interactions with the SP-B promoter-enhancer.** TTF-1 binds in distinct regions in the 5'-flanking sequence of the human SP-B gene. The proximal element (--to --80) contains two TTF-1 sites and activates transcription in concert with HNF-3 member by interacting with basal transcriptional apparatus of the SP-B gene. TTF-1 also binds to three distinct, clustered sites located from --439 to --331 that act as an enhancer influencing gene transcription from both the SP-B and SV40 promoters.

**TABLE I**

| Genes (species) | Core sequence | Location | Reference |
|-----------------|---------------|----------|-----------|
| SP-A (mouse)    | TCAAG         | --165 to --111 | 14        |
|                 | CTAAG         | --111 to --65  | 14        |
|                 | TTAA          | --65 to --25   | 14        |
|                 | TGAAG         | --25 to --10   | 14        |
|                 | TGAAG         | --10 to --7    | 14        |
| SP-B proximal (human) | TCAAG       | --70 to --100  | 4         |
| SP-B distal (human) | CCAAG       | --10 to --5    | Unpublished data |
| SP-B (mouse)    | CCAAG         | --10 to --5    | 25        |
|                 | CCAAG         | --5 to --1     | 25        |
|                 | CCAAG         | --1 to --1     | 25        |
| SP-C (human)    | CCAAG         | --10 to --16   | 25        |
|                 | CCAAG         | --16 to --28   | 25        |
|                 | CCAAG         | --28 to --41   | 25        |
| CCSP (mouse)    | GGAAC         | --302 to --278 | Unpublished data |
|                 | GGAAC         | --278 to --239 | Unpublished data |
|                 | GGAAC         | --239 to --180 | Unpublished data |
|                 | GCAAT         | --101 to --66  | Unpublished data |
by oligomerization of TTF-1 proteins through the Cys residues (13). Cooperativity of clustered protein-DNA binding sites was observed in ultrabithorax gene (15). POU family proteins (16) and homeobox containing human HOX 2.1 proteins (17) also bind to their cognate cis-active elements in a cooperative manner. The functional significance of these binding site clusters may lie in a fine tuning of a target gene regulation by limiting concentrations of the transcription factors. It is tempting to speculate that precise temporal-spatial regulation of TTF-1 concentration in the developing foregut endoderm may deter-

On the other hand, clusters of homeodomain regulatory proteins may provide potential interacting surfaces and facilitate contact with other nuclear proteins modulating gene expression. A region rich in glutamine and alanine is located C-terminal to the homeodomain region of the TTF-1 peptide (7). This sequence strongly resembles activator regions of other transcription factors. It is tempting to speculate that precise temporal-spatial regulation of TTF-1 concentration in the developing foregut endoderm may determine organ-specific gene expression and development of the lung and thyroid.

In general, upstream transcription activators are thought to interact with the basal transcription factor machinery. For example, the glutamine-rich activation domain of human SP1 interacts with Drosophila TAF110 (20), and the acidic activation domain of VP16 interacts with Drosophila TAF140 (21), as well as tumor suppressor protein p53 interacts with TAF140 and TAF160 (22), SP1, YY1, USF, CTF, and adenoviral E1A interacting with TAF155 (23), etc. The present findings demonstrate TTF-1-dependent enhancer activity in the distal upstream 5′ region of the SP-B promoter. From previous studies in this laboratory, the binding of TTF-1 proteins in region I of the SP-B gene was dependent upon interactions with general transcriptional factors in the SP-B promoter (4), functioning in a manner distinct from that of region II. Region I is indispensable for basal transcription of the SP-B promoter and does not act as an enhancer when linked to other basal promoters (4). In contrast, mutations in the TTF-1 binding sites in the distal element (region II) block TTF-1-dependent enhancer activity but do not block the activity of region I of the human SP-B promoter. It follows that the “extrinsic cooperativity” model described by Ptashne (24) may provide a mechanism explaining the distinct behavior of the distal and proximal hSP-B elements. Clusters of TTF-1 proteins in each region would increase the stability of the complex forming a higher order complex with the basal transcription factor machinery.

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