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The Gene Encoding the Hydrophobic Surfactant Protein SP-C Is Located on 8p and Identifies an *Eco*RI RFLP

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Summary

Pulmonary surfactant is composed primarily of phospholipids but also contains three known surfactant-specific proteins. These proteins are importnt in determining the physical properties of pulmonary surfactant—including its ability to adsorb to an air-liquid interface and its structure—but also appear to influence surfactant metabolism. We have previously assigned two surfactant proteins, SP-A (a 28-36-kDa glycoprotein) and SP-B (an 18-kDa hydrophobic protein), to the short arm of chromosome 10 and to chromosome 2, respectively. We now report that the gene encoding the 5-8kDa hydrophobic surfactant protein SP-C is located on the short arm of chromosome 8. A cDNA clone encoding the entire protein recognizes a useful *Eco*RI restriction-site-length polymorphism. Evaluation of congenital syndromes manifesting autosomal abnormalities does not further elucidate the functional role of this protein in promoting normal respiratory physiology.

Introduction

Pulmonary surfactant is composed primarily of phospholipid and protein. It is synthesized and secreted by alveolar type II epithelial cells and is responsible for the low surface tension at the air-liquid interface in the lung (King 1982). Deficiency of surfactant is the primary cause of hyaline-membrane disease (Avery and Mead 1959), and alterations in surfactant function may contribute to the physiologic abnormalities seen in the adult respiratory distress syndrome (Petty et al. 1977).

Although surfactant phospholipids are primarily responsible for lowering surface tension, at least three surfactant-specific proteins are probably essential for normal surfactant function. These surfactant proteins have been assigned the following nomenclature by consensus: SP-A, a glycoprotein with a reduced molecular weight of 28–36 kDa (King et al. 1975), SP-B, a hydrophobic protein with a nonreduced molecular weight of 18 kDa (Glasser et al. 1987; Hawgood et al. 1987), and SP-C, a hydrophobic protein with a nonreduced molecular weight of 5–8 kDa (Jacobs et al. 1987; Possmayer et al. 1987; Warr et al. 1987). Human cDNA clones for each surfactant protein have been isolated by several groups of investigators (Possmayer, in press). Deduced amino acid sequences from those clones demonstrate that each protein is structurally distinct. SP-B and SP-C are subject to amino and carboxy-terminal posttranslational proteolytic processing (Hawgood et al. 1987; Warr et al. 1987; Possmayer, in press).

Although the exact functions of surfactant proteins are unknown, the hydrophobic surfactant proteins SP-B and SP-C appear to enhance surface spreading of artificial mixtures of phospholipids (Hawgood et al. 1987). Surface spreading is also facilitated by the addition of SP-A to mixtures of phospholipids containing SP-B and SP-C individually or in combination (Hawgood et al. 1987). SP-A and calcium ions appear to be required for one physical form of surfactant, tubular myelin (Hawgood et al. 1985).

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Surfactant proteins also may have regulatory function in surfactant metabolism. Purified SP-A inhibits the stimulated secretion of phospholipid by type II cells in tissue culture (Dobbs et al. 1987). The presence of hydrophobic surfactant proteins in mixtures of phospholipids inhibits phospholipid synthesis by cultured type II cells (Thakur et al. 1986) while enhancing type II cell uptake of exogenous phospholipids (Claypool et al. 1984). Thus, surfactant proteins have important roles in regulating surfactant metabolism as well as in determining its physical properties.

To better understand the regulation and function of these proteins, we have previously localized coding sequences for SP-A to the long arm of chromosome 10 (Fisher et al. 1987) and coding sequences for SP-B to chromosome 2 (Emrie et al. 1988). We now describe the localization of sequences encoding SP-C to the proximal short arm of human chromosome 8, by using a well-characterized panel of somatic cell hybrids and a human/Chinese hamster ovary (CHO) hybrid constructed from a patient with a balanced t(3;8) translocation.

Material and Methods

Human/CHO-K1 cell hybrids were prepared from a series of fusions between several CHO-K1 auxotrophic mutants and different human fibroblasts or lymphocytes. The human chromosome content in these hybrids was characterized by both cytogenetic and isoenzyme techniques as described elsewhere (Jones et al. 1980, 1985; Inui et al. 1985). Cytogenetic analysis included sequential staining of the same metaphase preparations with trypsin banding and Giemsa-11 differential staining in sequential steps (Morse et al. 1982). Several hybrids were derived from well-characterized clones that lost defined portions of specific chromosomes. For example, R30–5B and R30–2A are derived from 706-B6 (Jones et al. 1981) and have lost 8pter-centromere and 8pter-q12, respectively. One hybrid independently derived contains only the short arm of chromosome 8. Another contains a translocated chromosome der(3) [t(3;8) (3qter→ 3p14.2::8p23.1 → 8pter)], which was previously described in a normal individual with a balanced 3:8 translocation (Kushnick et al. 1984). This hybrid was prepared by fusing lymphocytes containing a translocated chromosome with a CHO-K1 uridine auxotroph and selecting for the human Ura C locus on the long arm of human chromosome 3 by culture in uridine-deficient media. The identity of the translocated chromosome was confirmed by comparison of sequentially stained metaphase chromosomes, from somatic cell hybrids, with the donor karyotype.

Since some hybrid cells demonstrate chromosomal instability, DNA was purified within one or two passages of both cytogenetic and isoenzyme analysis. DNA was purified from hybrid cells by SDS–proteinase K digestion followed by sequential phenol-chloroform extractions and finally by ethanol precipitation (Jones et al. 1985). DNA was purified from anonymously donated blood obtained from the Bonfils Memorial Blood Bank as described elsewhere by Kunkel (Kunkel et al. 1978).

cDNA Probe for SP-C

A cDNA clone containing the entire 850-bp coding sequence for human SP-C was used as a probe (Warr et al. 1987). This clone is a gift of R. Tyler White and others, California Biotechnology, Mountainview. Its validity has been confirmed by complete nucleotide sequence analysis and comparison of the deduced amino acid sequence with the directly determined amino-terminal amino acid sequence of purified human SP-C (Warr et al. 1987). In these experiments the entire coding sequence was excised from its plasmid vector (pUC-19), purified on a Sea Plaque R® low-melting-temperature agarose gel and 32^P labeled using random oligonucleotide priming (Feinberg and Vogelstein 1983).

Southern Blot Hybridization

Purified DNA (20 μg from hybrid cells, 5 μg from human white blood cells) was digested with various restriction enzymes, using buffers recommended by the supplier. Complete digestion was reliably obtained by using a 4–6-fold excess of enzyme. Digests were resolved on a 0.8% agarose gel, denatured, and transferred to nitrocellulose membrane by capillary blotting. Nitrocellulose filters were baked at 80 C and then prehybridized and hybridized as described elsewhere (Fisher et al. 1987).

Results

SP-C Recognizes an EcoRI RFLP

When DNA digested with *Eco*RI from 10 random donors was subjected to Southern analysis using the entire SP-C coding sequence as a probe, two bands of hybridization, at 19.5 and 6.2 kb, are seen singly and in combination (fig. 1). On the basis of analysis of 20 unrelated individuals, the 19.5-kb allele is more common, with a frequency of 75%, while the 6.2-kb allele

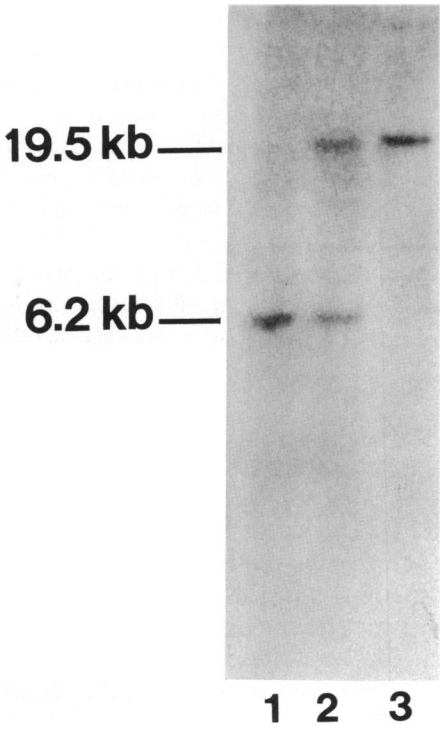

Figure 1 SP-C recognition of an *Eco*RI restriction-fragment polymorphism. Southern analysis of DNA from three individuals was digested with *Eco*RI and probed with SP-C. The individual in lane 1 is homozygous for the 6.2-kb allele, the individual in lane 3 is homozygous for the 19.5-kb allele, and the individual in lane 2 is heterozygous.

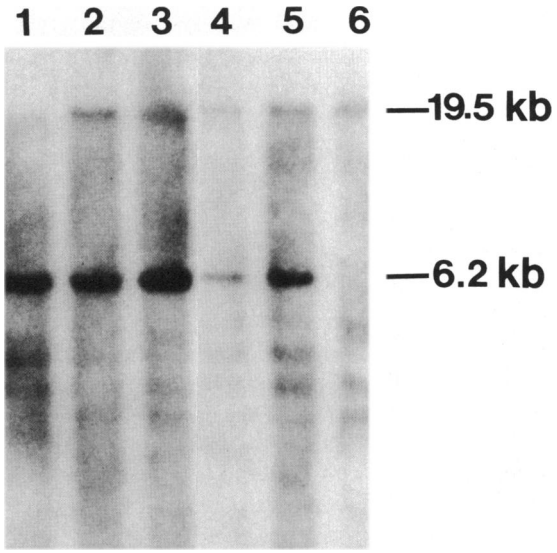

Figure 2 DNA blot analysis of 5 μg white blood cell DNA from two separate families that was digested with *Eco*RI and probed with a cDNA clone encoding SP-C. Lane 3 contains DNA from the progeny of lanes 1 and 2. One parent (lane 1) was homozygous for the 6.2-kb allele, and the other (lane 2) was heterozygous. The progeny (lane 3) was heterozygous. Lane 6 contains DNA from the progeny of lanes 4 and 5. The heterozygous parents (lanes 4 and 5) have resulted in an individual homozygous for the 19.5-kb allele. This data is consistent with codominant transmission of alleles.

occurs with a frequency of 25%. These findings are compatible with the idea that SP-C recognizes an *Eco*RI RFLP. Two families were evaluated for codominant transmission of alleles (fig. 2). Two crosses were observed in which one parent was heterozygous for both alleles while the other parent was homozygous for one allele, resulting in a heterozygous progeny. In another family the cross of two heterozygous parents resulted in a homozygous progeny. These data support the conclusion that these two bands arise as a result of RFLP. When *Eco*RI-digested DNA from somatic cell hybrids containing single versions of certain human chromosomes is probed, only one band is seen (fig. 3). Additionally, when DNA samples from individuals who are heterozygous for *Eco*RI bands is digested with *Kpn*I and subjected to Southern analysis, identical hybridization bands at 20 and 2 kb are observed (data not shown). Digestion with *Bam*HI, *Pvu*II, *Pvt*I, and *Hind*III yields identical hybridization patterns in all individuals tested. The sequence of one recombinant containing the human gene encoding SP-C does not contain any internal *Eco*RI restriction sites (R. T. White, personal communication). We believe that these experiments support the conclusion that the two *Eco*RI bands

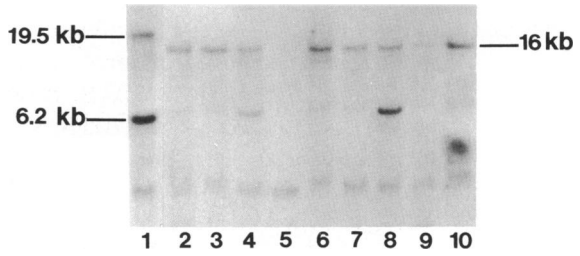

Figure 3 Southern analysis of somatic cell hybrids. DNA from a somatic cell hybrid mapping panel, digested with *Eco*RI and probed with SP-C. In lane 1, DNA from a human white-blood-cell DNA control shows two major bands at 19.5 and 6.2 kb. In lane 2, DNA from a CHO-K1 control shows a major band at 16.0 kb and a faint band at 6.5 kb. Hybrid DNA is contained in lanes 3–10. Lane 3, 822–1945; lane 4, 78–1; lane 5, 706-D1-R; lane 6, 706-D5–3; lane 7, 706-D5-A; lane 8, R-30–5E; lane 9, 762–8A; lane 10, 640–34-P6–1C. A 6.2-kb band is observed in lanes 4 and 8 and correlates, with 100% concordance, with the presence of 8p (table 1). Variable CHO-specific banding is occasionally seen (e.g., lane 5). With this hybrid there was aberrant banding with several enzymes; thus, CHO sequences homologous to SP-C must have been lost.

Table 1

Concordance Analysis of SP-C

	Human Chromosome																								
Cell Hybrid	SP-C	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	X	Y
640-77	−	−	−	−	+	−	−	−	−	+	−	−	−	+	+	−	−	−	−	−	−	−	−	+	−
826-26A	−	−	−	−	−	+	+	+	−	+	−	+	+	−	−	−	−	−	−	+	−	+	−	−	−
706-D5-3	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−
78-1	+	+	−	−	−	−	+	+	+	−	+	+	+	−	−	−	−	−	+	−	−	+	+	+	−
R30-5E	+	−	−	−	−	−	−	−	+	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−
762-8A	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	+
640-34-p6-1C	−	−	−	−	−	−	−	−	−	−	q	−	+	−	−	−	−	−	−	−	−	−	−	−	+
706-D1-R	−	−	+	−	+	−	−	−	−	−	−	−	+	+	−	−	+	+	+	−	−	−	+	−	−
706-D5-A	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−
822-19C15	−	+	+	+	−	+	+	−	−	−	+	+	−	−	+	+	−	+	−	+	+	+	−	−	−
976-20A	+	+	+	−	−	+	+	−	+	+	−	+	+	−	+	+	+	−	+	+	+	−	+	+	−
998-8	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+
971-38A	−	−	−	+	+	−	−	−	−	−	+	+	+	+	+	+	+	−	−	+	−	+	+	−	−
976-17B	−	+	−	−	+	+	+	−	−	+	−	+	−	+	+	+	+	−	+	+	+	+	+	−	−
R30-5B	−	−	−	−	−	−	−	−	q	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−
R30-2A	−	−	−	−	−	−	−	−	q	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−
87-075-2	+	−	−	−	−	−	−	−	p	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
86-077-34	−	−	−	q	−	−	−	−	p24	−	−	+	+	−	−	−	−	−	−	−	−	−	−	−	−
% Concordance		77	66	65	66	72	77	77	100	72	59	61	50	61	55	66	66	66	77	61	66	61	72	72	61

Note.—For calculation of concordance, fragments of chromosomes are not scored. SP-C maps to chromosome 8 having 100% concordance with an intact chromosome. Its hybridization with DNA from a hybrid cell containing 8p as the only human chromosomal material confirms an 8p location.

represent RFLP that arises from the loss of an *Eco*RI restriction site within the SP-C gene.

SP-C Is Localized to the Short Arm of Human Chromosome 8

A previously well-characterized panel of human/CHO somatic cell hybrids was used to localize coding sequences for SP-C. A representative Southern blot is demonstrated in figure 3. When DNA digested with *Eco*RI from this hybrid panel was probed with SP-C, bands were observed in the human control, at 19.5 and 6.2 kb. Faint bands are visible in CHO DNA at approximately 16, 10, 6.6, 4.2, 4.0, 2.5, and 2.4 kb. The 6.2-kb human band was visible only in hybrids that contain the short arm of chromosome 8. These data are compatible with the assignment of the sequences encoding SP-C to the short arm of human-chromosome 8. For a summary of hybridization results, see table 1.

Regional Location of SP-C on 8p

To more definitively localize SP-C to the short arm of chromosome 8, DNA from a somatic cell hybrid that contained a stable 8p as its only identifiable human material was probed with SP-C. A 6.2-kb band was visible when DNA from this hybrid was digested with *Eco*RI and subjected to DNA blot analysis (data not shown).

To regionally localize SP-C on the short arm of chromosome 8, a somatic cell hybrid constructed from a pateint with a familial 3:8 balanced translocation and segregating the translocated chromosome was probed with SP-C. Metaphase chromosomes from the human donor cell and hybrid cell are shown in figure 4. The various rearranged chromosomes 8 that are crucial for regional localization of SP-C to 8p are also shown. Since DNA from the hybrid containing a der(3) chromosome was negative for hybridization, SP-C is most likely centromeric from 8p23.1.

Discussion

When 10 human DNA samples digested with *Eco*RI were probed with SP-C, hybridization bands were observed at 19.5 and 6.2 kb. Family studies were consistent with the presence of an *Eco*RI RFLP. Segregation

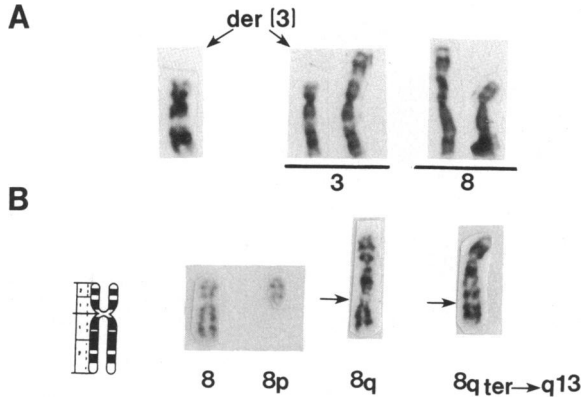

Figure 4 Morphology of chromosome 8 fragments used for regional mapping. *A*, Metaphase chromosomes 3 and 8 from a patient with a balanced translocation [T(3;8) (3qter 3 p14.2::8p23.1 8pter)] are shown . The der(3) chromosome from hybrid 86–077–34 is compared with that from the human donor. *B*, Schematic representation of chromosome 8 compared with the intact chromosome 8 from hybrids 78–1 and R30–5E, the 8p fragment from hybrid 87–075–2, and the long-arm fragments from hybrids R30–5B (8q) and R30–2A (8qter→q13), respectively. R3–5B and R30–2A are translocated to CHO chromosomes. Breakpoints are indicated with arrows and were determined by Giemsa-11 differential staining.

of the 6.2-kb band into somatic cell hybrids that contain one copy of chromosome 8 supports that conclusion. That the 19.5-kb band arises from variable presence of an *Eco*RI site is supported by the fact that *Kpn*I digests from these same individuals, when probed with SP-C, yield two bands at approximately 20 kb and 2 kb in all individuals. These observations mitigate against a large deletion as being the etiology of different band sizes. The 6.2-kb allele occurs with an approximate frequency of 25%, while the 19.5-kb allele occurs with a frequency of approximately 75%. Thus, this RFLP is sufficiently common to be useful in linkage analysis.

Using somatic cell hybrids, we have obtained hybridization data consistent with the localization of the 6.2-kb band to human chromosome 8. Hybrids R30–5B, R30–2A, and R30–5E are derived from the same primary hybrid that retained human chromosome 8 and human chromosome 14. Both R30–5B and R30–2A have lost the short arm of chromosome 8, while R30–5E contains an intact chromosome 8. Thus, the absence of SP-C hybridization with R30–5B and R30–2A DNA localizes SP-C to 8p. When DNA from an independently constructed hybrid cell containing the short arm of chromosome 8 as its only recognizable human chromosomal material was probed with SP-C, a human-specific hybridization band at 6.2 kb was observed. Thus, SP-C can be localized to the short arm of human chromosome 8. DNA digested with *Eco*RI from all somatic cell hybrids that segregated 8p contained the 6.2-kb SP-C allele, while none demonstrated the 19.5k-kb allele. CHO DNA digested with *Eco*RI demonstrates a 16.0-kb SP-C hybridization band that is sufficiently different in size from the human band to allow discrimination. Therefore, it is unlikely that our mapping experiments could have been confounded by a missed 19.5-kb band. Additionally, DNA from the mapping panel was digested with *Kpn*I and probed with SP-C. Only hybrids that contained 8p showed human-specific bands (data not shown). Therefore, we are confident that SP-C can be localized to 8p. To regionally localize SP-C, DNA from a hybrid segregating 8p23-pter translocated to 3p14.2 was probed with SP-C. No human-specific hybridization was observed. Therefore, SP-C can be localized centromeric from 8p23.

A review of the clinical syndromes associated with partial monosomies and trisomies of 8p (Rodewald et al. 1977; Borgaonokar 1984; de Grouchy and Turleau 1984) did not reveal any consistent or characteristic respiratory pathology. Since partial deletions, duplications, and mosaicism are common with 8p abnormalities, it is not possible to make definite statements regarding the effects of altered gene dose of SP-C on respiratory physiology.

In summary, we have localized SP-C to 8p23-cen by using a panel of somatic cell hybrids. We have also discovered a potentially useful RFLP for linkage analysis on 8p. We cannot make definite statements regarding gene dose for SP-C and abnormalities in respiratory function.

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