Peroxisome Proliferator-activated Receptor γ and Ligands Inhibit Surfactant Protein B Gene Expression in the Lung*

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Pulmonary nonciliated bronchiolar epithelial cells (Clara cells) and alveolar type II (AT II) epithelial cells are responsible for surfactant synthesis and secretion. These cells are highly lipogenic with a high lipid turnover rate. Although only 10% of surfactant lipids are neutral lipids, they play very important roles in maintaining pulmonary surfactant homeostasis. Many metabolic intermediate products of neutral lipids serve as ligands for various nuclear receptors that bind to target genes to influence gene transcription. In this report, the functional role of the neutral lipid metabolites, 15-deoxy-Δ12,14-prostaglandin J2 and 9-hydroxyoctadecanoic acids, and peroxisome proliferator-activated receptor γ was evaluated in surfactant protein B gene regulation. These reagents down-regulated surfactant protein B gene expression in respiratory epithelial cells at the transcriptional level in both cell line and whole lung explant systems. The studies support the concept that surfactant protein B homeostasis is influenced by neutral lipid metabolites in the lung.

During the respiratory cycles, the pulmonary surfactant protects the lung from collapse by lowering the air-liquid interface tension. Pulmonary surfactant is composed of 90–95% lipids and 5–10% surfactant proteins that are synthesized, stored, and secreted by alveolar type II (AT II) and nonciliated bronchiolar epithelial cells (Clara cells). Similar to the liver, the lung is an organ with a high lipid turnover rate to fulfill the need for surfactant synthesis. The majority of surfactant lipids are phospholipids (~80%). Disaturated phosphatidylcholine (PC), principally dipalmitoyl-PC, is the major phospholipid component in surfactant. In addition, there are about ~10% neutral lipids in pulmonary surfactant. Although extensive characterization of phospholipids has been performed in maintaining surfactant function and homeostasis, the functional roles of neutral lipids in the lung are less clear. It has been documented that many neutral lipid metabolites are the ligands for nuclear receptors that are potent transcription factors controlling gene regulation.

In neutral lipids, cholesteryl ester and triglycerides can be hydrolyzed by lysosomal acid lipase in the lysosome of cells to generate free cholesterol and free fatty acids (1). Free cholesterol and free fatty acid derivative compounds, hydroxyeicosatetraenoic acids, hydroxyoctadecanoic acids (HODEs), and 15-deoxy-Δ12,14-prostaglandin J2 (15d-PGJ2), are ligands for peroxisome proliferator-activated receptor γ (PPARγ). PPARγ binds to the nuclear receptor superfamily. PPARγ is involved in a broad range of physiological functions, including macrophage inflammatory responses (2, 3), adipocyte differentiation (4–6), glucose homeostasis (7), and apoptosis (8). Upon binding to ligands, PPARγ interacts with the retinoid X receptor (RXR) to form the PPARγ-RXR dimer that subsequently binds to specific PPAR-responsive elements (PPRE) on target genes and recruits nuclear receptor coactivators. Nuclear receptor coactivators possess intrinsic histone acetyltransferase activities to activate gene expression. PPARγ functions as both a positive and a negative regulator for target genes. Since AT II epithelial cells are responsible for synthesizing surfactant and highly lipogenic, it is important to know how gene expression of surfactant proteins in these cells is regulated by neutral lipid metabolic pathways.

Among the surfactant proteins, SP-B is a 79-amino acid amphipathic peptide that is synthesized and produced in Clara cells and AT II epithelial cells. SP-B is secreted from AT II epithelial cells along with phospholipids into the alveolar lumen to form the surfactant. SP-B facilitates lamellar body formation in AT II epithelial cells and phospholipid spreading during the respiratory cycles (9). Null mutations in the SP-B gene cause lethal respiratory distress in newborn infants and in SP-B-deficient mice produced by gene targeting (10, 11). Therefore, SP-B is essential for alveolar maturation and postnatal respiratory adaptation in newborns. Regulation of SP-B homeostasis is important to maintain the surfactant membrane structure and normal lung functions. Transcriptional regulation of gene expression is an important aspect of SP-B homeostasis. Elucidation of mechanisms by which SP-B gene transcription is controlled by positive and negative transcription factors and signaling molecules is critical to understand SP-B synthesis and physiological functions in the lung.

In this report, we assessed the effect of fatty acid metabolite 15d-PGJ2 on SP-B gene expression in respiratory epithelial cells and whole lung explants. The role of the downstream
mediator of this metabolite, PPARγ-RXRα, in regulating SP-B gene transcription was also studied. The studies support the concept that PPARγ-RXRα and its ligands serve as negative regulators for SP-B gene expression in respiratory epithelial cells. These studies add a new insight into the mechanism whereby SP-B gene expression and homeostasis are regulated by neutral lipid metabolites and nuclear receptors in the lung.

MATERIALS AND METHODS

Plasmids and Transgenic Mice—The mammalian expression vectors for wild type PPARγ and ACTR were kindly gifted from Drs. Ron Evans (the Salk Institute) and Karl Deisseroth (Yale University). The mammalian expression vector for dominant negative PPARγ was kindly gifted from Dr. Robert Malley. The bacterial expression plasmids for wild type PPARγ and RXRα were kindly provided by Dr. B. OMalley. The hSP-B 5’ luciferase reporter constructs were synthesized at the Salk Institute. The mammalian expression vector for dominant negative RXRα was kindly provided by Dr. B. OMalley. The hSP-B 1.5-kb luc gene transgenic mouse line was generated previously (13).

H441 Cell Maintenance—Human pulmonary adenocarcinoma H441 cells were originally obtained from American Type Culture Collection (ATCC) and cultured in RPMI supplemented with 10% fetal calf serum, glutamine, and penicillin/streptomycin. Cells were maintained and passaged weekly in 5% CO2 air.

RT-PCR—H441 cells were seeded and treated with 15d-PGJ2 (Cayman Chemical Co., Ann Arbor, MI) at a final concentration of 10 μM overnight. Total RNAs were isolated from cells using the RNA purification kit (Qiagen Co.), and RNA concentrations were determined. One μg of total RNAs from each sample was subject to RT-PCR assay using a pair of primers corresponding to the SP-B coding region and the GAPDH cDNA-specific primers was also used for RT-PCR. No significant change was observed in glyceraldehyde-3-phosphate dehydrogenase (GAPDH) expression in both control and test groups. The experiment was done in triplicate.

PPARγ Inhibition of hSP-B Transcription

**RESULTS**

**Inhibition of SP-B mRNA Expression by 15d-PGJ2 in H441 Cells**—To assess how endogenous SP-B gene expression is affected by neutral lipid metabolites, monolayers of H441 cells were treated with or without 10 μM 15d-PGJ2 overnight. Total RNAs were isolated from these cells. A pair of hSP-B cDNA-specific primers was used for RT-PCR assessment of hSP-B mRNA expression. As shown in Fig. 1, hSP-B mRNA expression was reduced by 15d-PGJ2 treatment in H441 cells. As a control, a pair of glyceraldehyde-3-phosphate dehydrogenase cDNA-specific primers was also used for RT-PCR. No significant change was observed in glyceraldehyde-3-phosphate dehydrogenase mRNA expression in both control and test groups. The experiment was done in triplicate.
lacZ adult AT II epithelial cells were isolated from hSP-B 1.5-kb transcriptional activity in primary AT II epithelial cells, and hSP-B 1.5-kb transcriptional activity in AT II epithelial cells was assessed whether neutral lipid metabolites affect the hSP-B system to study the hSP-B transcriptional activity–flanking regulatory sequence resides in AT II cells and hSP-B 1.5-kb 5’H11032 tissue- and cell type-specific manner (13). Since the hSP-B lacZ system, the hSP-B 1.5-kb regulatory region and the -flanking H11032 transgenic mouse system carrying an hSP-B 1.5-kb 5’-9-HODE in Primary AT II Epithelial Cells

For 4 days. Cells were lysed, and ~1 ng of protein was used for the β-galactosidase assay. The β-galactosidase activity of nontransgenic cells without treatment of ligands served as a control and was set as 1-fold. Values are means ± S.D. (n = 3).

dehydrogenase mRNA expression. Since the SP-B mRNA expression level can be affected at the transcriptional level or at the posttranscriptional level (mRNA stability and nuclear transportation), further studies are necessary to determine whether this inhibitory effect is a result of hSP-B transcriptional repression.

Inhibition of the hSP-B 1.5-kb lacZ Gene by 15d-PGJ2 and 9-HODE in Primary AT II Epithelial Cells—Previously, a transgenic mouse system carrying an hSP-B 1.5-kb 5’-flanking regulatory region and the lacZ gene was created. In this in vitro system, the hSP-B 1.5-kb lacZ gene recapitulates the endogenous SP-B gene expression pattern in the lung in a highly tissue- and cell type-specific manner (13). Since the hSP-B 1.5-kb 5’-flanking regulatory sequence resides in AT II cells and Clara cells in this transgenic mouse line, it is an ideal system to study the hSP-B transcriptional activity in vitro. To assess whether neutral lipid metabolites affect the hSP-B 1.5-kb transcriptional activity in primary AT II epithelial cells, adult AT II epithelial cells were isolated from hSP-B 1.5-kb lacZ gene transgenic mice and cultured in vitro. The next day, primary AT II epithelial cell monolayers were treated with or without a 10 μM concentration of either 15d-PGJ2 or 9-HODE. The nontransgenic AT II epithelial cells were also isolated and cultured in vitro as a control. After 4 days of incubation with 9-HODE, AT II epithelial cells were lysed and assayed for β-galactosidase activities. There was no significant difference between 15d-PGJ2- or 9-HODE-treated and nontreated AT II epithelial cells from nontransgenic mice. In contrast, a significant decrease in β-galactosidase activity was observed in 15d-PGJ2- or 9-HODE-treated AT II epithelial cells that were isolated from hSP-B 1.5-kb lacZ gene transgenic mice (Fig. 2, A and B). This result indicates that PPARγ ligands inhibit hSP-B gene expression at the promoter transcriptional level in AT II epithelial cells.

Inhibition of the hSP-B 1.5-kb lacZ Gene during Lung Branching Morphogenesis by 15d-PGJ2—Since expression of the hSP-B 1.5-kb lacZ gene is developmentally controlled as previously reported (13), the effect of neutral lipid metabolite 15d-PGJ2 on hSP-B 1.5-kb lacZ gene transcription was assessed in lung branching morphogenesis. Intact fetal lungs were isolated from hSP-B 1.5-kb lacZ transgenic mice at 11 days of gestation and cultured in vitro in the presence of X-gal. Nontransgenic fetal lungs were also isolated and cultured as a control. On the next day, lung explants were treated with or without 10 μM 15d-PGJ2 for 2 days. In nontransgenic control, no lacZ gene expression was detected in lung explants (Fig. 3). In hSP-B 1.5-kb lacZ gene transgenic mice, the in vitro cultured lung explant showed robust expression of the hSP-B 1.5-kb lacZ gene in newly formed epithelial tubules (Fig. 3). In contrast, hSP-B gene expression in branching epithelial tubules was significantly inhibited in the presence of 15d-PGJ2. This study indicates that 15d-PGJ2 can inhibit the hSP-B transcriptional activity during the developmental branching process. Suppression of SP-B gene expression seems not to affect the whole lung branching structure in this study. This is in agreement with the previous finding that ablation of the SP-B gene in mice does not affect embryonic lung development (10).

Inhibition of the hSP-B Gene by 15d-PGJ2 Is Mediated within the −218 to +41 Region—To define the cis-acting region that mediates 15d-PGJ2 inhibition on the hSP-B promoter, shorter hSP-B 500 and hSP-B 218 luciferase reporter constructs were tested in H441 cells by transient transfection and luciferase assay. The H441 cell line retains many characteristics of Clara cells. After 48 h of cell incubation with various concentrations of 15d-PGJ2, a significant decrease of both hSP-B 500 and hSP-B 218 luciferase activities was observed in H441 cells in a dose-dependent fashion (Fig. 4). In addition, a
Fig. 4. Inhibition of the hSP-B 500 and hSP-B 218 luciferase reporter genes by 15d-PGJ2 in H441 cells. Luciferase reporter gene constructs hSP-B 500, hSP-B 218, hSP-B(-500/−331), PGL2P, or PGL2P (0.5 μg) and 0.5 μg of pCMV-βgal vector were transfected into H441 cells. The next day, various concentrations (0, 5, 10, 20 μM) of 15d-PGJ2 were added to cells. After 2 days of incubation, cells were lysed, and luciferase activities were determined. The light units were assayed by luminometry. In each transfection, β-galactosidase activities were determined for normalization of transfection efficiency. Values are means ± S.D. (n = 3). ANOVA analysis showed a significant inhibitory effect of 15d-PGJ2 on hSP-B 500 and hSP-B 218 luciferase reporter genes (p < 0.05). ANOVA analysis also showed that moderate stimulation of 15d-PGJ2 on the hSP-B(-500/−331) PGL2P luciferase reporter gene was significant (p < 0.00).  

**PPARγRXRα Inhibits the hSP-B Gene Transcription**—The compound 15d-PGJ2 exhibits both PPARγ-dependent and independent mechanisms. To test whether PPARγ mediates the 15d-PGJ2 inhibitory effect on the hSP-B gene expression, a PPARγ and hSP-B luciferase reporter gene cotransfection study was performed in H441 cells. Monolayers of H441 cells were transiently transfected with the hSP-B 218 or hSP-B 150 luciferase reporter gene constructs. After subsequent 48-h cell incubation with 5 μM 15d-PGJ2, a significant decrease of both hSP-B 218 and hSP-B 150 luciferase activities was observed in H441 cells (Fig 5A). When hSP-B 218 or hSP-B 150 luciferase reporter gene constructs were co-transfected with various concentrations of PPARγRXRα, further inhibition was observed. This is a strong indication that PPARγRXRα mediates 15d-PGJ2 inhibition. To confirm this observation, a mutant PPARγ was chosen for the cotransfection assay. In the mutant, Leu468 and Glu471 in helix 12 of the ligand binding domain of PPARγ are mutated to alanine. The mutant retains ligand and DNA binding activities but exhibits no co-activator recruitment activity (20). When the hSP-B 150 luciferase reporter construct was cotransfected with increasing amounts of mutant PPARγ into H441 cells, no inhibitory effect was observed, Fig. 5B. Instead, a modest increase of the hSP-B 150 luciferase reporter gene activity was observed. This reversal of repression is probably due to the interference of endogenous PPARγ inhibitory effects by the mutant PPARγ protein.  

**PPARγ Expression in Mouse AT II Epithelial Cells and Clara Cells**—Since PPARγ can functionally inhibit SP-B gene expression, immunohistochemical staining was performed to test whether PPARγ is localized in AT II epithelial cells and Clara cells where SP-B is expressed and processed. Sections from adult mouse lungs were prepared and stained using an antibody against PPARγ. Sections were also stained with an antibody against thyroid transcription factor 1 (TTF1) as a positive control. TTF1 is a tissue- and cell type-specific marker whose expression is specifically restricted to AT II and Clara cells in the lung. Staining for TTF1 and PPARγ antibodies in mouse lungs was detected in bronchiolar and AT II epithelial cells where SP-B is synthesized (Fig 6) (13). In a negative control, no specific staining was detected by a FLAG antibody. Previously, RXRα expression was detected in AT II epithelial cells and Clara cells by immunohistochemistry (19). Therefore, PPARγRXRα not only functionally influences SP-B gene expression but also is colocalized physically with SP-B in the lung.  

**PPARγRXRα Does Not Directly Bind to the hSP-B (−150 to +41 Region)—**One mechanism for nuclear receptors to exert negative effect on gene transcription is to bind to cis-acting sites within the promoter region of the target genes and recruit corepressor complexes (21). To test whether the PPARγRXRα inhibitory effect is mediated by direct DNA binding to the hSP-B(-150 to +41) promoter region, the PPARγ-GST fusion protein was expressed in bacteria and purified by chromatography. The RXRα protein was prepared by in vitro transcription and translation. Two proteins were incubated with the 32P-radiolabeled hSP-B−150 to +41 bp fragment for EMSA in the presence of 15d-PGJ2. As shown in Fig. 7, the PPARγ-GST-RXRα complex did not form a protein-DNA complex with the hSP-B−150 to +41 promoter region. A homology search did not reveal the consensus sequence for PPRE in this region. In a positive control study, PPARγ-GST-RXRα formed a complex with a PPRe from the acyl-CoA oxidase gene, known to bind to PPARγRXRα. Therefore, the inhibitory effect of PPARγ and its ligands on the hSP-B gene is not mediated through direct DNA binding to the promoter region.  

**Reversal of the 15d-PGJ2 Inhibition by Nuclear Receptor Coactivator TIF2**—It has also been reported that PPARγ inhibi-
PPARγ inhibition of hSP-B transcription through the trans-repression mechanism by competing with a limited amount of the nuclear receptor coactivator pool in the cell (22). If PPARγ and its ligands inhibit the hSP-B transcription through the trans-repression mechanism, increasing the amount of nuclear receptor co-activators should reverse the inhibitory effect. To test this possibility, p160 family nuclear receptor co-activators, including SRC-1, ACTR, and TIF2, were co-transfected with the hSP-B 150 luciferase reporter construct into H441 cells to increase nuclear receptor co-activator concentrations. Without nuclear receptor co-activator cotransfection, 5 μM 15d-PGJ2 significantly decreased the hSP-B 150 luciferase activity in H441 cells (Fig. 8). When increasing amounts of TIF2 were cotransfected into H441 cells, the inhibitory effect of the hSP-B 150 luciferase reporter activity was reversed. The reversal effect was dose-de-
Effects of nuclear receptor coactivators on inhibition of the hSP-B 150 luciferase reporter gene by 15d-PGJ2 in H441 cells. Various amounts (0, 0.5, 1.0, 1.5, and 2.0 μg) of SRC-1, ACTR, and TIF2 expression vectors were co-transfected with the hSP-B 150 luciferase reporter gene construct (0.5 μg) and 0.5 μg of the pCMV-βgal construct into H441 cells. The next day, cells were treated with 10 μM 15d-PGJ2. After a 48-h incubation, cells were lysed, and luciferase activities were performed. In each transfection, β-galactosidase activities were determined for normalization of transfection efficiency. Values are means ± S.D. (n = 3).

DISCUSSION

Although there are only about 10% neutral lipids in pulmonary surfactant, their metabolites can serve as ligands to bind to various nuclear receptors to regulate surfactant protein gene expression. Prostaglandins are derived from fatty acids (primarily from arachidonate) through a series of biochemical conversions in vivo. In this report, we investigated the functional role of 15d-PGJ2, which serves as a ligand for PPARγ in SP-B gene expression in respiratory epithelial cells. Ligand 15d-PGJ2 inhibited endogenous SP-B mRNA synthesis in H441 cells (Fig. 1), indicating that the inhibitory effect can happen as early as 18 h. This apparently occurs at the gene transcriptional level, because expression of the lacZ reporter gene under the control of the hSP-B 1.5-kb 5′-flanking regulatory region was also inhibited by 15d-PGJ2 in primary AT II epithelial cells (Fig. 2). Using hSP-B promoter deletion constructs, the inhibitory effect was narrowed down to the hSP-B −150 to +41 bp promoter region (Fig. 5A). This region is highly conserved in both human and murine species (23). PPARγ-RXRα that mediates the 15d-PGJ2 action also inhibited hSP-B promoter transcription (Fig. 5, A and B). Endogenous expression of PPARγ was detected in both AT II and Clara cells in the mouse by immunohistochemical staining (Fig. 6). These results collectively suggest that PPARγ is colocalized with SP-B in both AT II epithelial cells and Clara cells and functionally influences SP-B gene expression.

Nuclear receptors exert negative regulation on gene regulation through various mechanisms. Some nuclear receptors repress transcription by binding to cis-acting sites within the promoter region of the target genes by recruiting corepressor complexes (21). In an EMSA study, the PPARγ-RXRα complex failed to bind to the hSP-B −150 to +41 promoter region that mediates the 15d-PGJ2/PPARγ inhibitory effect. Therefore, it is unlikely that this is the mechanism for PPARγ-RXRα and its ligands to inhibit hSP-B promoter transcription. A second mechanism involves nuclear receptor (e.g. PPARγ) transrepression through coactivator competition (22). Since there are limiting amounts of coactivators (CREB-binding protein/p300 and p160 coactivators including SRC-1, ACTR, and TIF2) in a given cell, nuclear receptors mutually antagonize each other by competing with these coactivators. In this mechanism, inhibition usually can be reversed by increasing concentrations of nuclear receptor coactivators in the cell. Indeed, cotransfection of nuclear receptor coactivator TIF2 caused the reversal of hSP-B gene inhibition by 15d-PGJ2 (Fig. 8). This was confirmed by the observation that a PPARγ mutant lacking the nuclear receptor coactivator recruiting ability reversed PPARγ inhibitory activity in H441 cells (Fig. 5B). The study suggests that there may be another unidentified transcription factor (e.g. nuclear receptor) in hSP-B −150 to +41 promoter region, which can recruit TIF2. In a similar situation, the sequestering of CREB-binding protein and SRC-1 by activated PPARγ accounts for transrepression of the inducible nitric-oxide synthase promoter in response to ligand binding (22). In this system, transrepression requires PPARγ interactions with LXXLL-containing coactivators through functional domains. It has been shown that a deletion of the ligand-dependent activation domain AF2 of PPARγ and point mutations of the critical charge clamp residues (PPARγ EA469 and KG301) weakened interaction with SRC-1 and CREB-binding protein. This deletion and point mutations led to complete loss of transrepression function (22). PPARγ transrepression has also been reported in cyclooxygenase-2 gene regulation (24).

SP-B gene expression is also subject to positive regulation by certain members of nuclear receptors. Previously, we have shown that RA and RAR transactivate SP-B gene transcription by recruiting nuclear receptor coactivators through an enhancer located in the hSP-B −500 to −331 region upon retinoic acid binding (18, 19). The formation of the transcriptional complex is dependent on RAR-RXR, TTF1, and nuclear receptor coactivators (18). Deletion of this highly conserved enhancer region abolished hSP-B gene expression in Clara cells and reduced its expression in AT II epithelial cells in transgenic mice (13). When a dominant negative RARα was overexpressed in H441 cells, this region is colocalized with SP-B in Clara cells and functionally influences SP-B gene expression.
cells, it strongly suppressed hSP-B transcription (25). In a doxycycline-inducible transgenic mouse system, overexpression of dominant negative RARs in respiratory epithelial cells caused abnormal alveolar formation in neonatal lungs, probably due to suppression of SP-B and other functional genes (25). To determine whether PPARγ interferes with RA/RAR transactivation in the hSP-B −500 to −331 enhancer region by coactivator sequestration, a chimeric hSP-B(−500/−331)/SV40 promoter was treated with 15d-PGJ2 in H441 cells. Interestingly, there was no transrepression observed (Fig. 4). Although the detailed mechanism is not clear at this moment, it seems that PPARγ and its ligands selectively compete with the nuclear receptor coactivator recruiting process in the hSP-B −150 to +41 promoter region but not with that in the hSP-B −500 to −331 enhancer region (Fig. 9). This selectivity must be determined by surrounding transcription factors and DNA cis-acting elements in the hSP-B 5′-flanking regulatory region. Whereas all p160 nuclear receptor coactivators stimulate hSP-B(−500 to −331)/SV40 luciferase reporter gene transcription (18), only TIF2 stimulated hSP-B 150 luciferase reporter gene transcription (data not shown). In agreement with this observation, only an increase of TIF2 concentration in H441 cells reversed the 15d-PGJ2 inhibitory effect of the hSP-B 150 luciferase reporter gene (Fig. 8).

PPARγ ligands also affect hSP-B temporal/spatial expression during lung branching morphogenesis. In lung explant in vitro culturing study (Fig. 3), hSP-B 1.5-kb lacZ gene expression was dramatically inhibited by PPARγ ligand treatment, implicating that the unidentified TIF2 recruiting factor in the hSP-B −150 to +41 promoter region is required for SP-B gene expression during lung development in newly formed epithelial tubules. This suggests that during lung development, both positive and negative regulation by nuclear receptors and coactivators are essential for proper SP-B gene expression. Previously, the glucocorticoid receptor has also been reported to inhibit hSP-B transcription (14), although the mechanism is unknown.

PPARγ has pleiotropic effects in various systems. There are studies suggesting that PPARγ plays a role in antagonizing proinflammatory response (3, 26–28). SP-B gene expression is stimulated by proinflammatory cytokines. We previously reported that SP-B gene expression is stimulated by proinflammatory cytokine interleukin-6 family cytokines in the lung. Interleukin-6 family cytokines stimulate downstream target genes by activation of signal transducers and activators of transcription 3 through tyrosine phosphorylation at Tyr705 (37). How PPARγ and its ligands affect this process of proinflammatory stimulation to keep the balance of SP-B gene expression during pro- and anti-inflammatory responses in the respiratory system is an important issue for future investigation and has potential clinical application.

In summary, neutral lipid metabolites in lipogenic AT II epithelial cells influence surfactant protein B gene expression and homeostasis in the lung. The inhibitory effect of PPARγ and ligands on SP-B gene expression represents a novel mechanism whereby SP-B homeostasis is regulated in respiratory epithelial cells. In pulmonary surfactant, phospholipids are the major structural component, whereas neutral lipid metabolites can serve as sensor signals to balance pulmonary surfactant homeostasis in responding to changes of various physiologic conditions and inflammatory responses in host defenses.

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