Pulmonary Surfactant Pathophysiology: Current Models and Open Questions

Pulmonary surfactant is an essential lipid-protein complex that stabilizes the respiratory units (alveoli) involved in gas exchange. Quantitative or qualitative derangements in surfactant are associated with severe respiratory pathologies. The integrated regulation of surfactant synthesis, secretion, and metabolism is critical for air breathing and, ultimately, survival. The goal of this review is to summarize our current understanding and highlight important knowledge gaps in surfactant homeostatic mechanisms.

The vital process of mammalian breathing is dependent on an extensive gas exchange surface provided by the alveoli in the lung periphery. Surface tension on the epithelial side of the air-blood barrier exerts a collapsing pressure that is stabilized by spreading of a lipid-rich film (pulmonary surfactant) at the alveolar air-liquid interface. Quantitative [e.g., respiratory distress syndrome (RDS)] or qualitative [e.g., acute RDS (ARDS)] changes in surfactant lead to alveolar collapse and the need for ventilatory support; likewise, accumulation of surfactant in the alveolar airspaces (e.g., pulmonary alveolar proteinosis) impedes gas exchange. Thus the integrated regulation of surfactant synthesis, secretion, and metabolism is essential for air breathing and, ultimately, survival.

Research in the past three decades has provided extensive insight into surfactant biology that, in turn, has facilitated development of surfactant replacement therapies: the latter have profoundly impacted the incidence of morbidity and mortality in newborn infants. However, despite the many remarkable achievements in this field, major questions remain unanswered. The goal of this review is to summarize our present understanding of surfactant homeostatic mechanisms and highlight important knowledge gaps in molecular pathways involved in surfactant synthesis, secretion, recycling, and degradation. This focus excludes discussion of the role of surfactant in innate lung defense, and the reader is referred to several excellent reviews of this topic (46, 57, 60, 109).

Synthesis and Assembly of Surfactant

The major components of pulmonary surfactant include phospholipids (~80%), neutral lipids (mainly cholesterol, ~10%), and the two hydrophobic peptides (1–2%) surfactant protein B (SP-B) and SP-C. Type II epithelial cells synthesize and assemble the lipid and protein components into complexes that are stored as tightly packed membranes in lamellar bodies until secreted into the alveolar airspaces (FIGURE 1). Molecular pathways involved in the regulation of expression, intracellular trafficking, and processing of the surfactant proteins have been extensively characterized; much less is known about the intracellular pathways regulating surfactant lipid biosynthesis.

Surfactant Proteins

Surfactant Protein B

SP-B is synthesized as a soluble proprotein that is processed to a smaller, lipid-associated peptide in the distal secretory pathway within the type II cell. Processing of proSP-B occurs in the multivesicular body (MVB) and lamellar body (LB) compartments and involves the action of napsin A, cathepsin H, and pepsinogen C (12, 37, 45, 96); at least one and perhaps several other as yet unknown enzymes participate in proprotein maturation. The fully processed, 79-amino acid mature peptide facilitates organization of surfactant membranes in the lamellar body, likely through its ability to promote membrane-membrane contacts, perturbation of lipid packing, and membrane fusion (49, 89). SP-B deficiency, arising from mutations in the human gene (SFTPB) or disruption of the mouse locus (Sftpb), results in vesiculated lamellar bodies with few or no bilayer membranes and electron dense inclusions. Most importantly, severe SP-B deficiency (i.e., >75% reduction in SP-B content in the airspaces) results in fatal RDS (19, 67, 70, 71). SP-B expression is altered in a number of acute and chronic lung diseases and may therefore contribute to pathogenesis (107). Thus identification of transcriptional pathways that modulate SP-B expression and proprotein maturation in both healthy and diseased lung remains an important area of investigation.

SP-B is also expressed in non-ciliated, bronchiolar epithelial cells (Clara cells). The proprotein is
not fully processed to the mature peptide in Clara cells, and the processing enzymes and fates of resulting peptides are largely unknown. Importantly, targetted expression of SP-B in type II epithelial cells but not Clara cells of Sftpb<sup>−/−</sup> mice is sufficient to rescue the neonatal lethal phenotype (62). Taken together, these data suggest that the function of SP-B in Clara cells is unrelated to surfactant homeostasis. Given the presence of saposin-like domains in the NH<sub>2</sub>- and COOH-terminal regions of the proprotein (77), it is possible that saposin-like peptides derived from these regions may play a role in innate host defense of the airspaces. Consistent with this hypothesis, a saposin-like peptide derived from the SP-B propeptide was recently identified in bronchoalveolar lavage fluid and alveolar macrophages. The peptide exhibited antimicrobial activity only at acidic pH, suggesting that it promotes killing of bacteria internalized by macrophages in the airspaces (112). Whether the saposin-like domain in the COOH-terminal region of the SP-B proprotein is also involved in alveolar defense remains to be established.

**Surfactant Protein C**

Unlike SP-B, SP-C expression in the lung is restricted to alveolar type II epithelial cells. Newly synthesized SP-C is an integral membrane protein in which the NH<sub>2</sub> terminus resides in the cytosol and the COOH terminus resides in the ER lumen (56). The cytosolic domain encodes information required for intracellular trafficking of SP-C to the MVB/LB compartments (20, 21, 54, 58). The COOH terminal, luminal domain may act as an intramolecular chaperone that transiently stabilizes the inherently unstable transmembrane domain (TMD), presumably until palmitoylation of two cytosolic cysteine residues assume this role (44, 52, 53). The identity of the palmitoyl acyltransferase that acylates SP-C is not known (93).

Like SP-B, SP-C is synthesized as a proprotein that is processed to a smaller, hydrophobic peptide in the MVB/LB compartments. The fully processed, 35-amino acid mature peptide consists of a TMD and a short segment of the cytosolic domain. Enzymes involved in the maturation of proSP-C have

![Figure 1. Biosynthesis of pulmonary surfactant](http://physiologyonline.physiology.org/)

**FIGURE 1. Biosynthesis of pulmonary surfactant**

Synthesis of the protein and phospholipid components of surfactant may proceed via separate pathways (green lines). SP-B and SP-C traffic through the Golgi and late endosome/multivesicular body (MVB) to the lamellar body. In contrast, surfactant phospholipids may traffic directly from the ER to the lamellar body; phospholipid transfer protein(s) (PLTP) and ABC transporters likely play an important role in phospholipid trafficking. (It is also possible that direct contact between the ER and lamellar body may facilitate phospholipid transfer; see text.) Transcriptional pathways involved in coordinated regulation of surfactant protein and phospholipid synthesis are indicated by black arrows. Surfactant components internalized from the airspaces may also contribute to biosynthesis (red lines). The micrograph of the multilayered surfactant surface film was modified from Ref. 88.
not been conclusively identified, although cathepsin H has been implicated (54), suggesting that the processing machinery may be shared with SP-B. The membrane localization of SP-C presents an interesting obstacle to its secretion. This conundrum is solved by internalization of the proprotein from the limiting membrane of the MVB to small luminal vesicles, an event that is regulated by Nedd4-2-mediated mono-ubiquitination of proSP-C (20, 58). Fusion of the MVB with a LB leads to SP-B-mediated incorporation of SP-C-containing luminal vesicles into existing surfactant membranes that are eventually secreted into the airspaces. Thus mature SP-C, one of the most hydrophobic peptides known, maintains its transmembrane orientation throughout biosynthesis.

Surprisingly, disruption of the SP-C locus in mice (Sftpc) has no overt effect on synthesis, trafficking, packaging, or secretion of surfactant by type II epithelial cells (40, 41). Sftpc−/− mice survive with essentially normal gas exchange apparently because SP-B is sufficient for surfactant function in vivo. However, SP-C deficiency is associated with development of chronic lung disease in humans (3) and strain-dependent, progressive lung disease in Sftpc−/− mice. Identification of genes that confer strain-dependent sensitivity and/or resistance to lung disease in Sftpc−/− mice remains an important and unresolved issue (44). Surfactant films from SP-C-deficient mice show minor intrinsic instability (40), which may contribute to chronic respiratory disease; however, it is equally possible that SP-C has an unidentified surfactant-independent function(s). Mutations in the SFTPC gene have been linked to chronic lung disease, possibly through formation of cytotoxic aggregates of mutant SP-C proprotein (for review, see Ref. 107). Overall, conservation of SP-C among species is consistent with an important function; however, despite considerable information about SP-C biosynthesis and in vitro surface activity, the role of this peptide in surfactant homeostasis and lung disease remains obscure.

**Synthesis of Surfactant Lipids**

**Phosphatidylcholine**

Phosphatidylcholine (PC) is a major component of all cellular membranes (98) and is the most abundant surfactant phospholipid (100). The rate limiting enzyme for PC synthesis, cholinephosphate cytidylyltransferase, is expressed as two isoforms (CCTα and CCTβ) encoded by separate genes. Targeted disruption of the CCTα locus (Pcylta) or the locus encoding another key enzyme in this pathway, choline kinase (Chka), results in embryonic lethality confirming that PC synthesis is essential for early embryogenesis (104, 110). Targeted deletion of Pcylta in type II epithelial cells of mice resulted in neonatal RDS and death within 10 min of birth (94). Lung development in Pcylta−/− mice was normal, but total PC content in the airspaces was dramatically reduced and formation of lamellar bodies in type II epithelial cells was highly aberrant. These results confirm the key role of the CCTα isoform in synthesis of surfactant PC.

Approximately half of the PC in surfactant is dipalmitoylphosphatidylcholine (DPPC; PC 16:0/16:0), accounting for ~40% of total surfactant phospholipid (82, 100). DPPC is the lipid considered as primarily responsible for the surface tension reducing properties of surfactant; therefore, regulation of this PC species is likely critical for surfactant homeostasis. Two pathways contribute to the production of DPPC, de novo synthesis and remodeling via lysoPC. The latter pathway accounts for up to 75% of DPPC in type II cells and involves deacylation of unsaturated PC at the sn-2 position by a calcium-dependent phospholipase A2 (33); peroxiredoxin 6, a calcium-independent phospholipase A2, may also contribute to deacylation of PC (25, 34). The enzyme responsible for re-acylation, lysophosphatidylcholine acyltransferase, was recently identified and named LPCAT1 (69). This finding is a significant achievement that will facilitate testing of a number of hypotheses in vivo. Targeted disruption of the LPCAT1 locus in type II epithelial cells will permit assessment of the importance of the remodeling pathway in surfactant homeostasis, identification of potential compensatory pathways, and the overall importance of DPPC for surfactant function in vivo. In addition, recent evidence supports the hypothesis that there is cross-talk between the remodeling and the de novo synthesis pathways (16). Identification of transcriptional networks that integrate expression of LPCAT1 and other lipogenic enzymes with surfactant proteins should provide important insight into the molecular pathways governing surfactant homeostasis (**FIGURE 1**).

**Phosphatidylglycerol**

The second most abundant surfactant phospholipid, PG, comprises ~10% of the surfactant lipid fraction in humans. This anionic phospholipid is not a common component of intracellular membranes (98). Unlike PC, surfactant PG content and molecular species vary significantly among animals (82). However, the overall content of anionic phospholipid (PG+Pi) is relatively constant, suggesting that the contribution of acidic polyhydroxylated phospholipids is more important than the precise molecular forms. A key step in PG synthesis is conversion of CDP-diacylglycerol to phosphatidylglycerol phosphate by phosphatidylglycerolphosphate synthase (8, 9). Transcription of the gene encoding this enzyme (PGSI) is increased threefold...
intracellular trafficking of surfactant phospholipids

The fully assembled surfactant lipid-protein complex is stored as tightly packed bilayer membranes in lamellar bodies of type II epithelial cells. Since lamellar bodies lack the requisite enzymes for phospholipid biosynthesis (8), surfactant lipids must be transported from the site of synthesis in the ER to the storage organelle. The identity of pathways involved in intracellular trafficking of surfactant phospholipids remains one of the major unanswered questions in this field. Transport of intracellular lipids can occur by at least three pathways, including vesicular transport, non-vesicular transport, and diffusion at membrane contact sites (98).

Vesicular transport clearly plays an important role in trafficking of newly synthesized surfactant proteins via the Golgi to the lamellar body (FIGURE 1). Vesicular transport is also important for recycling of surfactant components (both proteins and lipids) from the alveolar airspaces to the LB via the endocytic pathway. The biosynthetic and endocytic pathways converge at the MVB/late endosome (the boundary between these endosomal compartments is not well defined in type II epithelial cells). The internal membranes of MVBs are enriched in cholesterol and lyso-bisphosphatidic acid. Thus the endocytic recycling pathway is likely an important source of cholesterol and minor phospholipid components of lamellar body membranes (FIGURE 1).

In contrast to vesicular transport of surfactant lipids in the endocytic pathway, there is very little evidence for anterograde vesicular transport of DPPC or PG from the ER to the LB. Ultrastructural, autoradiographic analyses of type II epithelial cells in vivo detected the appearance of \(^{3}H\)choline-labeled lipids first in the ER followed by the Golgi and LB; notably label was not detected in the MVB (27). Although these results are consistent with trafficking of PC directly to the LB and/or via the Golgi, a separate study found that inhibition of vesicular transport through the Golgi did not inhibit incorporation of newly synthesized lipid into the LB (75). A unifying hypothesis posits that PC moves directly from the ER to the LB via a nonvesicular transport pathway. This hypothesis is supported by the localization of the ABC transporter, ABCA3, to the limiting membrane of the LB (68, 111). Disruption of the Abca3 locus results in neonatal lethal RDS associated with loss of mature lamellar bodies and a dramatic decrease in production of lung PG and PC (7, 26, 35, 48).

How is PC and/or PG transported from the ER to ABCA3 in the LB membrane? Intermembrane transport of PC and PG is significantly elevated in type II epithelial cells relative to whole lung and transfer activity increases commensurate with surfactant synthesis before birth (38, 63). Intracellular phospholipid transport activity was generally attributed to phospholipid transfer proteins and to PC-TP/StarD2 in particular. However, lung structure and function, including LB morphology and alveolar DPPC content, was unaffected in \(Pc-tp^{-/-}\) mice (97). This outcome was quite unexpected, given the specificity of PC-TP/StarD2 for PC (55) and its tempo-spatial relationship to surfactant synthesis. It is currently not clear whether compensation occurs in type II cells of \(Pc-tp^{-/-}\) mice or whether PC transfer is normally accomplished independently of PC-TP/StarD2. Other members of the START domain family (2) could account for PC transfer activity in type II epithelial cells, in particular StarD10. It is also possible that this function could be fulfilled by phospholipid transfer proteins lacking a START domain. SCP-2/nsL-TP and PI-TP both have PC transfer activity (108), and the former is enriched in type II epithelial cells and increases during fetal lung maturation (10). Overall, the involvement of phospholipid transfer proteins in nonvesicular transport of newly synthesized phospholipids from the ER to the LB remains an important and unresolved question.

Another possible mechanism for transfer of phospholipids between donor and acceptor membranes is via diffusion or facilitated exchange at membrane contact sites (98) (FIGURE 1). This transfer mechanism would likely require the participation of accessory proteins to ensure the formation of transient contact sites between the appropriate donor (ER) and acceptor (LB) organelles. It has been suggested that some phospholipid transfer proteins could fulfill the role of...
both accessory and transfer protein (2). Regardless of whether membrane contact is necessary for targeted transport of PC or PG from the ER to the LB, it is likely that a transfer protein(s) with docking motifs specific for each organelle would be required.

**Lamellar Body Maturation**

Based on the foregoing discussion, a simple model of lamellar body maturation can be constructed (FIGURE 1). The major surfactant phospholipids (DPPC, unsaturated PC, and PG) are synthesized in the ER. Because there is very little DPPC or PG in the ER, newly synthesized phospholipid must be rapidly exported from this organelle. Phospholipid transport is likely facilitated by specific phospholipid transfer proteins containing docking motifs that enable cargo loading at the ER and cargo discharge at the LB. Although phospholipid transfer proteins typically carry only a single cargo molecule, transfer can occur very rapidly (5). Import of PC and PG into the LB likely occurs through ABCA3. An excess of phospholipids at the inner leaflet of the LB membrane could drive the assembly of internal surfactant membranes (78). Incorporation of cholesterol and minor phospholipid components into surfactant membranes could be mediated by ABCA3, by unidentified lipid transporters in the LB membrane, or via the endocytic/recycling pathway. The process leading to highly organized, tightly packed surfactant membranes is poorly understood but likely requires SP-B and the fluidizing effects of cholesterol/minor phospholipids.

This highly simplified model raises numerous questions. Do newly synthesized minor surfactant lipid components employ the same transport machinery (i.e., phospholipid transfer proteins and ABCA3) as PC and PG? Are PC and PG carried by the same phospholipid transfer protein or are multiple carrier proteins involved? Is phospholipid import into the LB accomplished through more than one ABC transporter? Are elevated calcium levels in the LB required for packing of negatively charged (PG-rich) membranes and, if so, what is the molecular identity of the calcium pump? How is LB size (maturation) monitored/regulated? Proteomic analyses of the limiting membrane of the LB, currently underway in several laboratories (105), should identify candidate proteins that, in turn, may provide answers to these and related questions.

**Extracellular Surfactant**

**Reorganization of Surfactant Membranes in the Alveolar Airspaces**

Transition of the intracellular storage form of surfactant (bilayer membranes in LBs) to an extracellular functional surface film has been extensively studied but is only partly understood (78, 114). The alveolar epithelial cell surface is covered by a thin aqueous layer (hypophase) in which newly secreted, tightly packed surfactant membranes reorganize to form a loose network of interconnected membranes that contacts the air-liquid interface. It is not clear how the structural transformation of surfactant membranes is triggered, but potential effectors include changes in the hydration of surfactant complexes, pH, or calcium concentration (29–31, 78, 84, 85). Subsequently, SP-B and SP-C are thought to facilitate transfer of surface active molecules (particularly phospholipids and, most importantly, DPPC) from the membrane network to the surface film (see FIGURE 2) (79, 89). Although this model of interfacial adsorption is widely accepted, translation of the results of in vitro analyses to surfactant adsorption in vivo is not straightforward. In particular, most in vitro studies have used surfactant preparations that are significantly diluted (simulating unpacked surfactant membranes) and simplified (i.e., simple phospholipid mixtures) compared with newly secreted surfactant. Moreover, the cellular microenvironment (composition and volume of the hypophase) may profoundly influence transfer of phospholipids from the packed membrane state to the surface film (33). In this regard, the results of recent studies revealed that packed surfactant membranes (similar to newly secreted surfactant) can spontaneously adsorb and rapidly transfer surface active material into the air-liquid interface, apparently without passing through an unpacked state (29, 47). Thus the mechanisms by which newly secreted surfactant phospholipids are transferred to the air-liquid interface in vivo remains an open question.

**Composition and Function of the Surface-Active Film**

Cyclical expansion (inhalation) and contraction (exhalation) of alveoli lead to changes in alveolar surface area accompanied by altered surface tension. Early work by Clements (19a) proposed that surface tension must be <2 mN/m at low lung volumes to prevent alveolar collapse (atelectasis) and rise to a maximum of 20–25 mN/m at higher volumes to maintain alveolar stability. This goal is achieved by maintenance of an interfacial film highly enriched in DPPC, a saturated phospholipid that produces extremely low surface tension on film compression (<1 mN/m). The lack of fluidity of pure DPPC films at body temperature is overcome by incorporation of phospholipids with unsaturated acyl chains and cholesterol into surfactant complexes and the interfacial film (10a, 27a, 30a, 68a). Observation of surfactant films by epifluorescence or atomic force microscopy suggests that satu-
rated phospholipids (DPPC) segregate into ordered micro- and nano-domains, which can be highly compressed to produce the requisite low surface tension; unsaturated phospholipids and surfactant proteins remain in disordered regions that facilitate rapid transfer of phospholipids into (and out of) the surface film (22a, 27a, 115). Commingling of ordered and disordered domains thus provides a potential mechanism for maintenance of a stable interfacial film.

Although we have a basic understanding of surfactant film dynamics, many details of the underlying processes remain unclear. It is assumed that DPPC enrichment of the surface film is required to support maximal pressures (very low surface tensions) at end expiration, but the actual proportion of DPPC that reaches the interfacial film is not known. Some studies suggested that SP-B and SP-C could selectively promote insertion of DPPC (99) into the interfacial film, but direct proof for this activity is lacking. It has been also proposed that compression of the surface film during expiration induces progressive refining of the interfacial film by squeezing out less stable unsaturated species, leading to DPPC enrichment (28, 64, 76). Direct examination of the structure and composition of the surface film formed from native surfactant under physiologically relevant conditions is required to confirm or discard these hypotheses. It is currently thought that the ability of surfactant to produce very low tensions during breathing is dependent on formation of a multilayered film at the interface (6, 36, 88). However, a comparison of the rheological properties of multilayered vs. monolayered surfactant films is required to test this model. Finally, an active line of research has tried to assign specific activities to SP-B and SP-C in remodeling of interfacial surfactant films during compression and facilitating film re-spreading during expansion (see FIGURE 3). Consistent with the neonatal lethal phenotype of SP-B-deficient mice, in vitro approaches using devices that capture some of the physiological compression-expansion constraints of the respiratory interface revealed that SP-B is required to achieve and sustain the lowest tensions during compression. SP-C, on the other hand, may cooperate in facilitating interfacial surfactant dynamics, including folding of the surface film, maintaining the multilayer reservoir attached to the interface during compression and promoting efficient re-spreading of the film on expansion. Optimal performance of surfactant at the interface may therefore require cooperation of both hydrophobic surfactant proteins (1). Validation of these models in vivo requires the development of new genetically modified animal models that are not yet available.

**Surfactant Recycling and Surfactant Homeostasis**

Compression-expansion cycling leads to progressive conversion of the surface active fractions of

![FIGURE 2. Pulmonary surfactant adsorption to the interface and surface film formation](image_url)

Processes that may contribute to transport of surface active surfactant species to the interface include 1) direct cooperative transfer of surfactant from secreted lamellar body-like particles touching the interface, 2) unraveling of secreted lamellar bodies to form intermediate structures such as tubular myelin (TM) or large surfactant layers that have the potential to move and transfer large amounts of material to the interface, and 3) rapid movement of surface active species through a continuous network of surfactant membranes, a so-called surface phase, connecting secreting cells with the interface.
Surfactant into much less active lipid/protein complexes (43, 95). Inactivation probably includes detachment of small particulate entities from the interface, changes in lipid/protein organization, and oxidation of lipid and protein species on repetitive exposure to air (83). Surfactant may also be inactivated by incorporation of materials inhaled from the upper airways or leaked from capillaries (42, 114). Maintenance of a fully functional surfactant film therefore requires continual film refinement through efficient removal of spent surfactant and incorporation of newly secreted complexes. It remains unclear whether the distinct surfactant structures that coexist in the alveolar pool are specifically targeted to functional, recycling, or clearance pathways.

Surfactant homeostasis requires coordinated regulation of the processes summarized in FIGURE 1. The alveolar surfactant pool is continuously depleted through cellular uptake by type II epithelial cells and alveolar macrophages as well as removal via the mucociliary escalator. It is unclear whether cellular uptake of alveolar surfactant occurs indiscriminately or whether there is selective targeting of specific forms of surfactant to type II cells for recycling and/or macrophages for degradation. Preliminary support for selective uptake of alveolar surfactant by type II cells comes from recent studies in SP-D-deficient mice (50, 51). Interaction of the collectin SP-D with PI-rich surfactant complexes altered surfactant structure and enhanced uptake by type II cells but not macrophages. Thus, in addition to its well documented role in host defense, SP-D plays an important role in regulating alveolar pool size.

The loss of surfactant from the airspaces is balanced by secretion of surfactant stored in lamellar bodies: regulation of surfactant secretion is therefore critical for homeostasis. Several excellent, recent reviews provide a comprehensive analysis of surfactant secretion and the central role of calcium mobilization in this process (4, 29). However, although pharmacological and physical stimuli of surfactant secretion have been extensively characterized,

![FIGURE 3. Participation of proteins SP-B and SP-C in surfactant dynamics during respiratory compression-expansion cycling](image-url)

Hydrophobic surfactant proteins play key roles in facilitating optimal dynamic behavior of surfactant during breathing. During exhalation, the surfactant surface film folds through three-dimensional transitions, forming a complex structure that sustains maximal pressures. Protein SP-C facilitates compression-driven folding of surfactant interfacial films (1), expulsion of lipids and lipid/protein complexes from the interface (80, 92), and formation of three-dimensional phases (59, 101, 102). SP-B stabilizes the interfacial film (2) and promotes establishment of membrane-membrane contacts (22, 24, 86), leading to formation of multilayered membrane arrays (3) (17). SP-B seems to provide mechanical stability to compressed films (23), possibly through increasing cohesivity between surfactant layers during maximal compression of the surface film. SP-C could promote association of excluded surfactant structures with the maximally compressed interface, likely through its NH2-terminal segment and/or insertion of palmitoylated cysteines of the protein into tightly packed interfacial films (4) (11, 102). Finally, both SP-B (23, 90, 106) and SP-C (73, 74, 81) seem to promote insertion (5) and re-spreading (6) of phospholipids from subsurface compartments into the interface during expansion.
the molecular pathway(s) linking changes in alveolar pool size to stimulation of secretion has not been identified.

Depletion of the intracellular pool of surfactant via the secretory pathway is balanced in part by uptake and recycling of alveolar surfactant in type II cells. Recycling is not sufficient to replenish the intracellular pool because some internalized surfactant is degraded; how internalized surfactant is partitioned between the recycling and degradation pathways remains an important unresolved question. To maintain intracellular pool size, new synthesis of surfactant must be coupled to recycling. Surfactant pool size also varies significantly with age, the alveolar pool being much larger in neonates than in adults (18, 50, 113). Overall, maintenance of the balance between the intracellular storage pool and the functional alveolar pool requires tight integration of synthesis, secretion, recycling, and degradation. How these pathways are modulated in response to quantitative and/or qualitative changes in alveolar surfactant remains a large and important knowledge gap.

In summary, although much has been learned regarding the composition and function of surfactant, virtually nothing is known about the transcriptional networks that integrate molecular pathways involved in prenatal type II cell maturation, surfactant protein and lipid synthesis, and alveolar defense. How these molecular networks “sense” alveolar pool size in the postnatal lung and modulate transcriptional pathways to balance surfactant synthesis with surfactant secretion, recycling, and degradation is completely unknown. Likewise, it is unclear to what extent regulatory networks involved in type II cell maturation are also involved in alveolar repair and reconstitution of surfactant homeostasis following lung injury. These critical knowledge gaps are reflected in the paucity of new therapies for lung immaturity and chronic lung diseases.

Research in the laboratories of the authors is currently supported by grants from Spanish Ministry of Science (BIO2009-09694, CSD2007-0010), Community of Madrid (S0505/MAT/0283), and Universidad Complutense to J. Perez-Gil and The National Heart Lung and Blood Institute (HL-056285 and HL-086492) to T. E. Weaver.

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