Surfactant protein B: unambiguously necessary for adult pulmonary function

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In the report from Melton et al., one of the current articles in focus (Ref. 21, see p. L543 in this issue), they use genetically engineered mice to demonstrate that at least 25% of normal surfactant protein B production is required for adult pulmonary function. With the use of doxycycline-regulated, compound-conditional knockout murine lineages, the authors show that genetic disruption of surfactant protein B synthesis causes adult respiratory failure due to loss of surface activity of the pulmonary surfactant. This observation suggests a method for stratification of adult respiratory failure phenotypes based on surfactant protein B quantity and function and provides additional rationale for treatment of adult respiratory failure with surfactant replacement. The evolutionary conservation of surfactant protein B supports its unambiguous requirement for adult pulmonary function demonstrated by Melton et al. Experience in newborn infants with surfactant replacement therapy and with surfactant protein B deficiency provides lessons to shape these strategies.

The pulmonary surfactant system, a complex mixture of lipid and protein, evolved when vertebrates began air breathing between 320 and 420 million years ago (5). Fossil records suggest a common, air-breathing ancestor for all vertebrates (6). In nonmammals, especially those without diaphragms, the pulmonary surfactant likely functions as an antiadhesive to ensure reexpansion of large gas-exchanging units (faveoli) after compression by forces like birth or ingestion of a relatively large food source (5). In mammals, the pulmonary surfactant is required for maintenance of the lung’s gas-containing, aqueous-lined alveoli and minimization of work of breathing during regular volume changes (5). The striking evolutionary conservation of surfactant protein B is demonstrated by studies of the Australian lungfish Neoceratodus forsteri, one of the most primitive surviving air-breathing vertebrates: antibodies to human surfactant protein B identify surfactant protein B-like peptides in lamellar body-like organelles of pulmonary epithelium in this species (26). Structural similarities between surfactant protein B and other members of the amoebapore superfamily suggest that its function in these early vertebrates may have been antimicrobial (1, 31). However, its conservation during mammalian evolution is likely due to its unique and irreplaceable role in the surface activity of the pulmonary surfactant of air-breathing mammals.

Among the four known surfactant-associated proteins (A, B, C, and D), surfactant protein B is unique in evolutionary and functional characteristics. Although similar in hydrophobicity and surface activity to surfactant protein C (29, 30), surfactant protein B probably arose considerably earlier in evolution than surfactant protein C. Unlike the hydrophilic surfactant proteins A (also detectable early in pulmonary evolution) and D, surfactant protein B is surface active: it contains 5 amphiphilic alpha-helices that interact with the surfactant lipid monolayer to reduce breakup of anionic lipid headgroups during the folding transition of the pulmonary surfactant’s phospholipid monolayer and loss of these same headgroups to the subphase upon monolayer collapse (10, 19). Surfactant protein B also lowers surface tension by disrupting attractive forces between water molecules (19). The evolutionary conservation of surfactant protein B and its surface tension-lowering characteristics in air-breathing mammals both predict a critical role in adult lung function. Melton et al. (21) confirm this prediction in mice. Clinical experience with newborn infants provides evidence of the potential benefits and limitations of using surfactant protein B in evaluation and treatment of adults with respiratory failure.

After pioneering work by von Neergard, Pattle, and Clements (reviewed in Ref. 10), Avery and Mead first reported the importance of the pulmonary surfactant for successful fetal-neonatal pulmonary transition in 1959 (3). With the use of a Langmuir-Wilhelmy balance to compare surface tension-lowering capacity of saline extracts of lungs from premature infants who had died of hyaline membrane disease and more mature infants who died from other causes, they showed that lungs of premature infants lacked surface-active material and thus established the biochemical defect that accounts for significant pulmonary mortality and morbidity in prematurely born infants. Further studies by Gluck et al., Klaus et al., and King and Clements (reviewed in Ref. 10) led to recognition of the importance of disaturated phospholipid (specifically, dipalmitylphosphatidylcholine) for function of the pulmonary surfactant and identification of four surfactant-associated proteins (A, B, C, and D). In 1980, Fujiwara et al. reported the initial uncontrolled trial of bovine surfactant replacement in prematurely born human infants with severe respiratory failure that suggested the efficacy of this approach (7). Subsequently, several large studies...
documented the safety and efficacy of surfactant replacement for prematurely born infants with respiratory failure (17). Despite the likely mechanistic heterogeneity of surfactant deficiency in these patients, surfactant replacement with surfactant protein B-containing preparations has been associated with significant improvement in survival, especially among white infants (14, 17). Although definitive pathophysiological studies are lacking, infants who fail to respond to surfactant replacement therapy are at significantly greater risk of death in the newborn period and exhibit increased pulmonary vascular permeability of gallium-68-labeled transferrin measured by positron emission tomography (12, 23). Surfactant replacement did not alter vascular permeability (23). This experience, along with the data from Melton et al. (21), strongly suggests that surfactant replacement with surfactant protein B-containing surfactant preparations may provide a potentially useful method for treatment of causes of adult respiratory failure that disrupt the pulmonary surfactant function or reduce its production without overwhelming disruption of alveolocapillary integrity. Although an initial trial with aerosolized, protein-free surfactant replacement showed no benefit, subsequent studies using bronchoscopic administration of protein-containing surfactant preparations have shown both physiological and biochemical improvement (2, 9, 27, 28). Although developmental disruption of surfactant protein B production in infants and possibly acute respiratory distress syndrome in adults can be successfully treated with surfactant replacement, genetic disruption in infants provides a significantly different therapeutic challenge.

In 1993 and 1994, Nogee et al. (23, 24) reported two full-term infants in a single family who lacked surfactant protein B due to homozygous, frame shift loss-of-function mutations in codon 121 of the surfactant protein B gene (the 121ins2 mutation). These studies established the unambiguous necessity of surfactant protein B for function of the pulmonary surfactant and for successful human fetal-neonatal pulmonary transition. Subsequent studies have demonstrated that the 121ins2 mutation is the most frequently observed loss-of-function mutation in this gene and accounts for ~65% of all loss-of-function alleles (29). More than 20 additional loss-of-function mutations have been identified (25, 29). Studies have also established an unambiguous genotype-phenotype correlation: infants born with genetic disruption of the surfactant protein B gene develop progressive respiratory failure in the neonatal period and expire within months of birth. This correlation has been observed in infants from multiple ethnic backgrounds. No asymptomatic infants have been observed in large, population-based studies (4, 25). This experience suggests that no molecular, genetic, or biochemical redundancy for the functions of surfactant protein B exists in humans. In contrast to the clinical benefit observed in prematurely born infants treated with surfactant protein B-containing surfactant preparations, surfactant protein B replacement in infants with genetically disrupted surfactant protein B expression does not reconstitute function of the pulmonary surfactant (11). This failure is likely due to the intracellular requirement for surfactant protein B peptide fragments generated during normal proteolytic processing of the proprotein (42 kDa) to the mature, secreted protein (8 kDa) (18). Lung transplantation is currently the only available therapeutic option for infants with genetically based surfactant protein B deficiency (13).

Melton et al. (21) find that like newborn mice and human infants, adult mice have an unambiguous pulmonary requirement for surfactant protein B production: when surfactant protein B production is turned off, mice develop lethal respiratory distress associated with loss of function of the pulmonary surfactant. These studies, along with experience from evolution, newborn infants, and previous human and animal studies, suggest that causes of adult respiratory failure that disrupt surfactant protein B production or function may benefit from surfactant replacement therapy with surfactant protein B-containing preparations. This therapeutic strategy deserves further prompt investigative evaluation. Use of surfactant protein B-containing surfactant replacement may provide an important clinical probe to identify distinct surfactant protein B-dependent and -independent mechanisms for adult respiratory failure. Surfactant responsiveness may indicate intact but inhibited surfactant protein B expression, and unresponsiveness may suggest regulatory or structural genetic defects in surfactant protein B expression or overwhelming disruption of the alveolocapillary membrane. The data from Melton et al. also suggest that surfactant protein B quantification in bronchoalveolar lavage may be a clinically useful strategy for stratification of adult pulmonary diseases: a threshold of 25% of normal surfactant protein B concentration in bronchoalveolar lavage may identify patients who would benefit from surfactant replacement therapy regardless of the mechanism of pulmonary surfactant disruption. Such studies are likely to lead to improved understanding of respiratory failure and improved patient outcomes.

DISCLOSURES

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REFERENCES