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Interstitial lung disease and surfactant dysfunction as a secondary manifestation of disease: insights from lysosomal storage disorders

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Lysosomal storage disorders are a group of genetic metabolic disorders caused by dysfunctional endosomal-lysosomal hydrolases, altered vesicular trafficking or biogenesis of the lysosome. This results in the accumulation of partially degraded substrates within cells, leading to abnormalities in multiple organ systems and reduced life expectancy. These diseases are chronic and progressive with the more severe cases experiencing the onset of disease symptoms early in life. These symptoms include skeletal, joint, airway and cardiac manifestations. Many of the lysosomal storage disorders exhibit significant respiratory issues, which frequently appear to affect pulmonary surfactant metabolism leading to an increased morbidity. Interstitial lung disease (ILD) refers to a group of disorders involving the airspaces and tissue compartments of the lung. The major categories of ILD in children that present in the neonatal period include developmental disorders, growth disorders, pulmonary surfactant dysfunction disorders, and specific conditions of unknown etiology unique to infancy. The purpose of this review is to examine the commonalities between lysosomal storage disorders with respiratory pathology and interstitial lung diseases. Increased awareness of the commonalities may instigate a more thorough investigation of symptoms thus providing an accurate and timely diagnosis enabling more precise treatment that will improve patient wellbeing.

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Introduction

There is mounting evidence that pulmonary surfactant dysfunction is central to the pathology of interstitial lung diseases (ILD), both in children (chILD) and in adults [1,2]. Nevertheless, a large subgroup of ILD is classified as idiopathic, that is, of unknown cause. Moreover, pulmonary surfactant dysfunction is also implicated in the respiratory pathology that manifests during disease progression in a number of lysosomal storage disorders (LSD) [3,4], a group of approximately 70 genetic metabolic disorders [5] predominantly caused by dysfunctional endosomal-lysosomal hydrolases, but also caused by alterations in proteins in-

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volved in vesicular trafficking and the biogenesis of lysosomes [6]. These defects result in the accumulation of substrate that would have otherwise been degraded in the endosome-lysosome system [6]. LSDs are not considered classic respiratory diseases, however a large number of these disorders do have respiratory manifestations secondary to the primary pathology [7–9]. These patients suffer from recurrent respiratory infections challenging their already compromised health and wellbeing. This observation further emphasises the concept that the etiology of lung disease is often indirect and can be caused by a range of systemic diseases such as collagen vascular diseases and acute respiratory distress syndrome and a range of organ-specific diseases, including renal, hepatic, gastrointestinal, neuromuscular, cardiovascular and endocrine and metabolic [10]. The pathological mechanisms of ILDs involving components of the pulmonary surfactant system (i.e. surfactant proteins and lipids), their altered biogenic pathways and homeostasis and their biophysical structure and function at the air-liquid interface of the lung have been established through the use of animal models [2,11–14]. This review considers the evidence concerning the link between interstitial lung disease and lysosomal storage disorders, and the involvement of the pulmonary surfactant system.

Interstitial lung disease

Interstitial lung disease is a collective term describing greater than 200 disorders that affect pulmonary tissue (parenchyma) and airspace. Patients display diffuse parenchymal lung alterations, which may include the alveoli, airways, blood vessels and pleura. This can be caused by genetic disorders or epithelial cell stress due to infection, radiation and environmental exposures resulting in apoptosis, inflammation and fibroblast proliferation which culminates in aberrant repair of the epithelial and mesenchymal cells [2].

Genetic disorders of surfactant production and function cause significant lung disease in children, primarily via deficiencies in surfactant proteins (SP) -B and -C, which result in changes in alveolar and interstitial development [2,15]. Furthermore, mutations in the ATP-binding cassette sub-family A member 3 (ABCA3) gene [16], an important lipid transporter, result in severe respiratory distress in newborns requiring immediate intervention. ABCA3 dysfunction has also been identified in the milder form of ILD in older children, adolescents and adults [2,17]. The diagnosis of chILD is made following intensive investigation and includes clinical evidence of hypoxemia, non-specific abnormalities identified in chest radiographs, lung function testing with characteristic hyperinflation and obstruction, echocardiogram sometimes showing evidence of pulmonary hypertension and blood studies covering genetic abnormalities, immune dysfunction, auto antibody studies and environmental dust exposures [18].

It has long been held that the dysfunction of pulmonary surfactant is implicated in chILD [1,19,20], however, ILD is rarely associated with inherited SP deficiency in adults. Pulmonary fibrosis is the largest subtype of ILD and also the most common associated with adults. Idiopathic pulmonary fibrosis (IPF) is defined as a specific form of chronic, progressive, fibrosing interstitial pneumonia of unknown cause, but associated with epithelial cell stress. The normal homeostasis of the alveolar epithelial cell is disrupted following damage resulting in apoptosis, inflammation and fibroblast proliferation, affecting the repair of cells with excess collagenous fibrotic deposits in the interstitium [2]. The IPF group of lung diseases is further graded as usual interstitial pneumonia (UIP), probable UIP, indeterminate for UIP and alternate diagnosis [21] following investigative CT scans. Guidelines for the further investigation of IPF are followed according to the initial CT outcome, with a standardised format approved by the American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), and Latin American Thoracic Society (ALAT) [21]. Commonly in chILD, adolescent and adult ILD there is evidence of impaired gas exchange, which is due to dysfunction of surfactant homeostasis in the alveolar compartment.

Role of surfactant in respiratory dysfunction

Pulmonary surfactant is a surface-active mixture of lipids and proteins, which lines the alveolar surface of the lungs. It is synthesised in alveolar epithelial type II (AEII) cells and stored in lamellar bodies, which are modified intracellular lysosomal organelles or secretory lysosomes [22] (Fig. 1). Chemical and mechanical stimuli of the AEII cells promote the secretion of surfactant from lamellar bodies into the fluid lining of the lung to form a lipoprotein film at the alveolar air-liquid interface [23]. Pulmonary surfactant has a dual role: it functions to regulate the interfacial surface tension of the lung during the breathing cycle to reduce the work of breathing and in host defence as part of the innate immune system of the lung, where it protects against pulmonary-acquired pathogens [23].

Pulmonary surfactant is comprised predominantly of phospho- and neutral lipids, which make up greater than 90% of the surfactant. The most abundant phospholipid is phosphatidylcholine (PC), of which two-thirds exists in the fully saturated form as dipalmitoylphosphatidylcholine (DPPC), which facilitates the reduction of surface tension during the respiratory cycle [24]. The balance of phospholipids includes phosphatidylglycerol (PG), phosphatidylserine (PS), phosphatidylinositol (PI), sphingomyelin (SM) and bis-(monoacylglycero) phosphate (BMP). Neutral lipids (NL) and cholesterol comprise the remaining lipids, the latter providing fluidity to the phospholipids, which facilitates surfactant

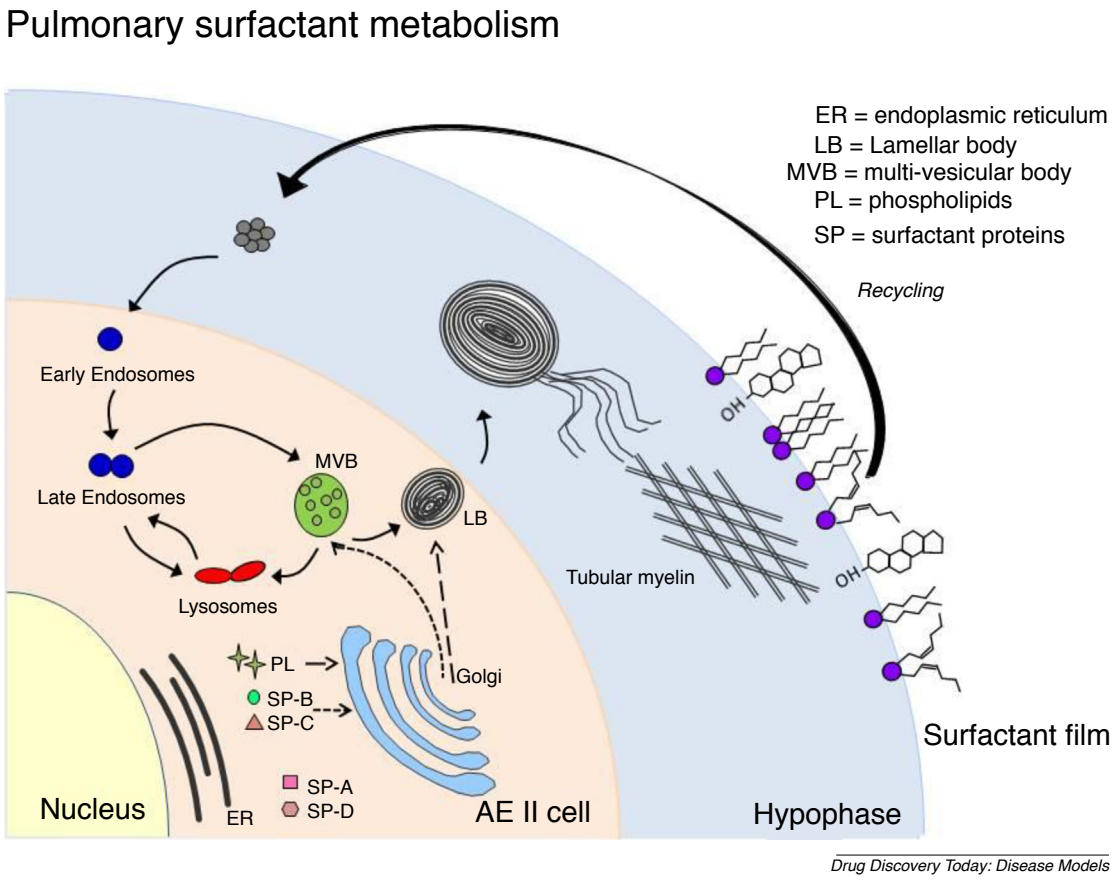

Fig. 1. Surfactant synthesis and secretion. Surfactant proteins are transported from the endoplasmic reticulum to the Golgi apparatus. Surfactant proteins B and C are packaged into multi-vesicular bodies and stored in lamellar bodies. Surfactant proteins A and D are secreted directly into the hypophase. Phospholipids are transported to lamellar bodies, which are then released into the hypophase. Lamellar bodies unravel into a cross-hatched structure called tubular myelin which supplies the surfactant film at the air-liquid interface. Small fractions of lipids and proteins are recycled via endocytosis through the endosome-lysosome system where they combine with new surfactant lipids and proteins in multi-vesicular bodies to be stored in lamellar bodies [Adapted with permission from [76].

film reordering and provides film dynamics during inspiration and expiration [25,26]. Finally, four surfactant proteins (SP), -A, -B, -C and -D make up ~8% of the pulmonary surfactant [12].

Surfactant proteins -B and -C combine with phospho- and neutral lipids to provide structural integrity to the interfacial film. Synthesised in the endoplasmic reticulum they are transported by multi-vesicular bodies to be packaged in lamellar bodies. In response to mechanical and/or chemical stimuli lamellar bodies are secreted into the liquid lining, i.e. the hypophase, where they unravel to form a tubular myelin network from which the pulmonary surfactant film is derived [27] (Fig. 1). SP-B interacts with SP-A and is critical to the formation of the tubular myelin network of surfactant [28]. Furthermore, SP-B is the only essential surfactant protein as SP-B deficiency is incompatible with life in both neonates and mouse models [29]. SP-C is required for optimal surface activity in the pulmonary surfactant film, and whilst not critical for life, changes in SP-C structure and function have been associated with interstitial lung diseases [30].

Surfactant proteins -A and -D are produced in AEII cells and secreted to the hypophase, where they play an important role in innate immune function [31]. SP-A and -D are active in preventing infection by binding to complex polysaccharides and lipopolysaccharides on the cell surface of pathogens, thus modulating cytokine and chemokine release, activating macrophages and initiating phagocytosis [31,32]. These SP's are members of the collectin family of proteins, the role of which is to enhance pathogen clearance by one of three different modes: via opsonisation and aggregation, as an activation ligand or by the upregulation of cell surface receptors to increase microbial recognition [33]. Opsonisation and aggregation occur as a result of the interaction between collectins and bacteria, viruses or allergens leading to the identification of the pathogen, and their uptake by immune cells including alveolar macrophages, monocytes, neutrophils and dendritic cells [33].

Lysosomal storage disorders

Lysosomal storage disorders (LSD) are a group of inherited chronic metabolic diseases that result from the disruption in the breakdown and recycling of cellular components in lysosomal organelles, the major organelle in the cellular degradation cycle [34,35]. This group of over 70 different disorders can be classified into five major classes based on the type of primary storage molecule: mucopolysaccharidoses, sphingolipidoses, glycoproteinoses (oligosaccharidoses), lipidoses and other LSD including multiple enzyme deficiency, lysosomal transport defects and glycogen storage disease [36]. Each disease is caused either by a dysfunctional acidic lysosomal hydrolase that is normally involved in the degradation of substrate within cells, or by defects in lysosomal membrane proteins or in soluble non-enzymatic lysosomal proteins, which results in the accumulation of partially degraded material. In addition, there is frequently secondary accumulation of lipid in the endosome-lysosome system [34]. This accumulation can cause secondary disruptions of other biological and cellular functions thus increasing the severity of the disease [6,34,37].

Symptoms of LSD include hydrocephalus, organomegaly, short stature, corneal clouding, enlarged tongue, cardiac disease, kyphosis, deafness, spinal cord compression, hepatosplenomegaly, neurological impairment, coarse facial features, sleep apnoea, obstructive and restrictive lung disease and respiratory infections [34,38–40]. Many of these symptoms can contribute to respiratory compromise in the individual. The structure and function of the upper respiratory tract and trachea may be affected by increased deposition of stored substrate. Musculoskeletal compromise will affect the thoracic cage and diaphragm and hepatosplenomegaly may compromise lung function [41]. Although each individual LSD is relatively rare, a recent report suggests a collective incidence of approximately 1 in 2315 live births [42]. Therefore, this group of diseases is considered a serious health issue, although the severity ranges from mild to severe in individual cases [6,40]. The more severe disease cases have profound effects on the patient, with a requirement for increased care and case management. In the most severe cases of LSD, death occurs before the age of 10 years [43].

Respiratory dysfunction in LSD

Significant respiratory pathology manifesting as interstitial lung disease or exhibiting dysfunction of pulmonary surfactant metabolism has been demonstrated in several LSD where the accumulation of lipid and other substrates have been identified (Table 1). Furthermore, these patients suffer from recurrent respiratory infections, suggesting a compromised pulmonary innate immune system. These diseases include the mucopolysaccharidoses (MPS), Sandhoff disease, Gaucher, Niemann-Pick types A and C2, Sialadosis and Hermansky–Pudlak syndrome (HPS) [7,8,44–49]. Moreover, there is evidence that several of the LSD have not only an increase in secondary lipid storage, but a consequential alteration in the production of pulmonary surfactant leading to respiratory distress [7,8]. For example, there has been evidence of increased SP-A and phospholipids in Niemann Pick type C2, which may contribute to respiratory compromise [3]. Respiratory manifestations in the mucopolysaccharidoses have also been noted [41], but have not been specifically investigated, with the exception of our recent, as yet unpublished work [49–51].

Table 1. Lysosomal storage disorders with documented respiratory dysfunction involving alterations in pulmonary surfactant, molecular storage affected and pathology sample.

Disease	Pulmonary pathology	Pathology sample
Mucopolysaccharidosis	↑ GM3 accumulation	Lung tissue
(MPS) IIIA	↑ Bis-(monoacylglycero)phosphate	Lung tissue
[49–51]	↓ Cholesterol	Bronchoalveolar lavage (BAL)
	↓ Bis-(monoacylglycero)phosphate	
Sandhoff	↑ GM2 accumulation	Lung tissue
[7,47]	↑ Phosphatidylcholine	BAL
	↑ Phosphatidylethanolamine	
Gaucher	↑ GM2 accumulation	Lung tissue
[7,47]	↑ Phosphatidylcholine	BAL
Niemann Pick C	↑ Sphingomyelin	Lung tissue & BAL
[3,8]	↑ Cholesterol	
	↓ Phosphatidylcholine	
	↑ SP-A	
Sialidosis	↑ Phosphatidylcholine	BAL
[47]		
Hermansky-Pudlak	↑SP-B, SP-C	Lung tissue
[74]	↓SP-B, SP-C	BAL
	↑Phospholipids	Lung tissue

Intracellular lysosomal storage has also been linked to a change in autophagy, a mechanism used by the cell to break down normal cell structures due to stress. Alterations in this process compromise the normal balance of pro- and anti-inflammatory factors, which are required to eliminate invading pathogens, while maintaining a healthy cellular environment [52]. In addition the accumulation of lipid substrates can lead to macrophage activation and cytokine release thus stimulating inflammatory responses [53]. Changes in the inflammatory response in many LSD together with changes in the pulmonary surfactant system suggests that inflammation may also be associated with respiratory dysfunction in mucopolysaccharidosis IIIA (MPS IIIA). This is currently being investigated in our laboratory [50,51] using a naturally occurring MPS IIIA C57BL/6 congenic mouse model with the deficient *N*-sulfoglucosamine sulfohydrolase (SGSH) gene resulting in approximately 3% sulphamidase activity, closely mimicking the pathological, biochemical and behavioural characteristics observed in humans [54].

The mucopolysaccharidoses, of which there are seven subgroups, are caused by defective glycosaminoglycan (GAG) catabolism resulting in the accumulation of partially degraded GAG in the lysosome [40]. Respiratory manifestations with severe obstruction in upper and lower airways in MPS I, II, V and VI patients, and to a lesser extent in MPS IIIA patients have been reported [41,55]. Primary lung involvement is not normally a symptom reported at birth in the MPS, however, there are several recently documented cases where neonatal respiratory dysfunction was reported for both MPS IIIA and MPS I. For example, symptoms of respiratory distress requiring ventilation, tachypnea, intercostal in-drawing and interstitial lung anomalies were evident in a patient that was diagnosed with MPS IIIA following a biopsy at a later age [56]. Similarly, neonatal interstitial lung disease with symptoms of respiratory distress requiring intubation was evident at birth in a patient later diagnosed with MPS I [57]. Our own recent work using a naturally occurring MPS IIIA C57BL/6 congenic mouse model [49,50,54] has shown changes in composition which impacts on the functionality of pulmonary surfactant [50]. We were prompted to pursue these studies, due to the fact that a range of other classes of LSDs have demonstrated surfactant alterations (Table 1).

Sandhoff disease, a variation of the GM2-gangliosidoses and defective in the lysosomal hydrolase, β-hexosaminidase, is characterized by an accumulation of the ganglioside GM2 and GA_2 glycosphingolipid [58,59]. There is evidence of increased phosphatidylcholine in pulmonary surfactant in the Sandhoff mouse model (the Hexb -/- mouse) [7,60]. Sandhoff patients initially present with regressed development, followed by sight and hearing impairments, behavioural problems, seizures, hepatosplenomegaly, and severe neurological manifestations. Bronchopneumonia and resultant respiratory dysfunction frequently occurs and leads to death [7].

Gaucher disease is one of the most common types of LSD which occurs due to a deficiency in the lysosomal enzyme, gluco-cerebrosidase, resulting in the accumulation of excessive lipid material in lungs, liver, spleen, kidneys and bone marrow [61,62]. This is reflected in the D409V/null mouse model exhibiting glucosylceramide accumulation in the lung [62]. The disease is also associated with respiratory problems due to infiltration of alveolar, interstitial and peribronchial spaces by lipid loaded-macrophages (Gaucher cells) often showing evidence of the ground-glass presentation on CT scan [63]. Prognosis of Type 2 Gaucher disease patients is very poor and most die due to cardiac and respiratory failure [63,64].

Patients with Niemann-Pick type C2 present with respiratory distress, jaundice and hepatosplenomegaly early in infancy. Clinical manifestations may also present in late adulthood as interstitial lung disease [65]. The disease is also associated with other abnormalities of the lung parenchyma involving inflammation and fibrotic alterations within the lung tissue [66]. Mutations in the NPC2 gene in Niemann Pick type C2 hinder the binding of unesterified cholesterol [67] and transportation of cholesterol to phospholipid vesicles [68]. Investigation into the pulmonary system of Niemann Pick type C2 (129/C57Bl6/BALBC) mice has shown an accumulation of enlarged foamy alveolar macrophages and enlarged lamellar bodies [3,48]. The composition of pulmonary surfactant was changed in that there was a reduction in the percentage of the surface-active lipids phosphatidylcholine, phosphatidylglycerol and phosphatidylinositol and an increase in the percentage of cholesterol, glucosylceramide, ceramide and sphingomyelin. A significant increase of SP-A was also reported in the animal model [3,8]. Furthermore, a recent case study with a diagnosis of Niemann Pick type C2 displayed an abnormal accumulation of surfactant, macrophages and cholesterol in the airspaces, characteristic of alveolar proteinosis, a recognized ILD [8].

Sialidosis is caused by α-*N*-acetyl neuraminidase deficiency resulting from a mutation in the neuraminidase gene. Patients present with gait abnormalities, decreased visual acuity and myoclonus that commences with intention tremors and difficulty with fine motor movements, before developing to include leg tremors and possible seizures [69]. Patients are affected by frequent respiratory infections that can lead to death [47]. An abnormal intracellular accumulation of phosphatidylcholine, along with an abundance of macrophages with vacuolated cytoplasm and lysosomes with irregular granular lamellar structures in surfactant have been reported in sialidosis patients [47,70].

Hermansky–Pudlak syndrome (HPS) is caused by mutations in the β3A subunit of the AP-3 adaptor, affecting protein transport to the lysosome from the Golgi apparatus [44–46,71]. HPS is associated with fibrotic lung disease, which is evidenced by abnormal pulmonary function tests pointing

to restrictive lung pathology [44,46,71]. Previous morphological studies have indicated the presence of large lamellar bodies in AEII cells of the HPS1/2 (ep/pe) mouse model, with evidence of patchy fibrotic lung tissue and enlarged airspaces [72–74]. Increased expression of SP-B and -C in lung tissue, but a decreased content of phospholipids and SP-B and -C in BAL have been reported compared with the wild type murine samples. This would suggest an alteration of the composition and therefore function of pulmonary surfactant [74].

Conclusion

This review aimed to raise awareness and emphasise the importance of recognising the possible contribution of lung parenchymal abnormalities and the occurrence of interstitial lung disease in many lysosomal storage disorders. The clinical awareness and continued scientific investigations are critical for the recognition of early symptoms thus providing an accurate and more timely diagnosis and hence treatment that will improve the quality of life experienced particularly by the more severely affected patients. Extensive use of LSD mouse models has advanced the description of the pathology and metabolism of respiratory compromise associated with each model. In all of these diseases there is a suggestion of an alteration in the composition of pulmonary surfactant due to changes in phospholipid metabolism and the accumulation of lysosomal storage material leading to functional and ultrastructural modifications. There is also evidence of changes in the pulmonary surfactant protein composition in LSD. Together this suggests that there may be a similar underlying subcellular mechanism occurring in the AEII cells, responsible for alterations in the lipid and protein composition of pulmonary surfactant in all LSD. Although respiratory manifestations are considered a secondary pathology in LSD, it is likely that with improvements in neuronally-targeted therapies, other, formerly less dominant systemic pathologies, such as interstitial lung disease, may become more critical as patient survival rates increase. As we increase our understanding of the associated molecular mechanisms we may uncover potential new therapeutic targets to develop adjunct therapies for the treatment of interstitial lung disease in lysosomal storage disorders.

Declarations of interest

None.

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