Systematic review of drug effects in humans and models with surfactant-processing disease

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Drug effects in disease models of surfactant-processing disease are highly dependent on mutation
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ABSTRACT Fibrotic interstitial pneumonias are a group of rare diseases characterised by distortion of lung interstitium. Patients with mutations in surfactant-processing genes, such as surfactant protein C (*SFTPC*), surfactant protein A1 and A2 (*SFTPA1* and *A2*), ATP binding cassette A3 (*ABCA3*) and Hermansky–Pudlak syndrome (*HPS1*, *2* and *4*), develop progressive pulmonary fibrosis, often culminating in fatal respiratory insufficiency. Although many mutations have been described, little is known about the optimal treatment strategy for fibrotic interstitial pneumonia patients with surfactant-processing mutations.

We performed a systematic literature review of studies that described a drug effect in patients, cell or mouse models with a surfactant-processing mutation. In total, 73 articles were selected, consisting of 55 interstitial lung disease case reports/series, two clinical trials and 16 cell or mouse studies. Clinical effect parameters included lung function, radiological characteristics and clinical symptoms, while experimental outcome parameters included chemokine/cytokine expression, surfactant trafficking, necrosis and apoptosis. SP600125, a c-jun N-terminal kinase (JNK) inhibitor, hydroxychloroquine and 4-phenylbutyric acid were most frequently studied in disease models and lead to variable outcomes, suggesting that outcome is mutation dependent.

This systematic review summarises effect parameters for future studies on surfactant-processing disorders in disease models and provides directions for future trials in affected patients.

Introduction

Idiopathic interstitial pneumonias (IIPs) are a rare group of diseases characterised by distortion of lung interstitium. IIPs can be subclassified into fibrotic interstitial pneumonia (FIP), smoking-related interstitial pneumonia and acute/subacute interstitial pneumonia [1]. The aetiology of IIPs is unknown; however, affected patients commonly have a first-degree relative with pulmonary fibrosis, referred to as familial interstitial pneumonia. It has been suggested that up to 20% of FIP cases might be familial [2, 3]. In FIP, two distinct groups of causal genetic mutations have been recognised; surfactant-processing and

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telomere maintenance gene mutations. To date, mutations in four surfactant-associated genes have been found to cause pulmonary fibrosis: surfactant protein C (*SFTPC*) [4, 5], surfactant protein A1 (*SFTPA1*) [6], surfactant protein A2 (*SFTPA2*) [7, 8] and ATP binding cassette transporter (*ABCA3*) [9, 10]. Furthermore, mutations in Hermansky–Pudlak syndrome 1 (*HPS1*) and 4 (*HPS4*) can cause pulmonary fibrosis in patients with Hermansky–Pudlak syndrome (HPS) with a lung phenotype equalling that of FIP [11, 12]. In addition, it has been found that Hermansky–Pudlak syndrome 2 (*HPS2*, associated with mutations in gene *AP3B1*) can cause pulmonary fibrosis in children and only results in mild interstitial lung disease (ILD) in adults [13]. *SFTPC*, *SFTPA1* and *SFTPA2* encode surfactant proteins (SPs)-C, -A1 and -A2, respectively, that have various biophysical functions and protect alveoli against damage and infection [14, 15]. The genes *ABCA3*, *HPS1*, *AP3B1* and *HPS4* encode structural proteins of lamellar bodies, the characteristic organelles in alveolar type II cells (AEC2) that are crucial for surfactant processing [16–18]. In general, mutations in surfactant-processing genes seem to cause misfolding or inappropriate localisation of proproteins, which leads to accumulation of proprotein in the endoplasmic reticulum or in inappropriate cellular compartments or in degradation of the proprotein [19]. In turn, this results in altered cellular processes in AEC2, such as dysregulated proteostasis, altered surfactant lipid composition and activation of immune cells in *SFTPC* non-BRICHOS mutations [20, 21], endoplasmic reticulum stress in *SFTPC* BRICHOS mutations and *SFTPA1* and *2* mutations [22–26] and impaired lipid transport, dysfunctional lysosome-related organelles, increased endoplasmic reticulum stress and apoptotic signalling in *ABCA3* and *HPS* mutations [17, 27–29]. In addition to the above disease-causing mutations, single nucleotide polymorphisms in the *MUC5B* and *TOLLIP* genes have been associated with predisposition to idiopathic pulmonary fibrosis (IPF), as well as survival in IPF patients [30–32]. Recent studies have identified various molecular phenotypes in IPF patients. These different molecular phenotypes correspond to variance in disease behaviour, and possibly to the response to different treatment regimens. Stratification of FIP patients based on genetic characteristics as well as cellular and molecular biomarkers could lead to personalised treatment strategies in the future [33, 34]. However, previous therapeutic trials have mostly not tested what genetic characteristics and biomarkers are associated with a good treatment response. Therefore, it is not known whether FIP patients with surfactant-processing mutations should receive the same therapy as other FIP patients. They might benefit from a different treatment strategy.

The aim of this systematic review is to provide an overview of studies that investigated drug effects in patients, cell or mouse models containing a mutation in surfactant-processing genes involved in pulmonary fibrosis. This review will focus on drug types, effect parameters and outcomes. This will provide a basis for future research efforts into treatment strategies for FIP patients with surfactant-processing mutations.

Materials and methods

Data sources and literature searches

A literature search in the electronic databases of Pubmed and Embase was performed with the help of a clinical librarian. We selected studies that contained, in the Medical Subject Headings (MeSH), keywords or text words, at least one search item from each of the following three groups: 1) ILD, with MeSH terms referring to ILD or lung cells; 2) surfactant-processing mutation, with MeSH terms referring to genes involved in adult FIP, pulmonary surfactant-associated protein, Hermansky–Pudlak syndrome or ATP-binding cassette transporter; 3) treatment, with MeSH terms referring to drug, treatment or therapy. The search was restricted to articles written in English and published before July 2, 2017. In the Embase search, conference abstracts were excluded. To maximise the inclusion of case reports/series, a second search was performed. This search included search items from groups 1 and 2, but not group 3 (treatment). This second search was restricted to the categories case report, clinical article, clinical study, clinical trial (phase I–IV), (classical) article, cohort analysis, comparative study, controlled study, controlled clinical trial, human, human tissue, major clinical study, retrospective study, evaluation study, letter, multicentre study, observational study, pragmatic clinical trial and randomised control trial. Duplicates within the search with two search items and the search with three search items were identified and removed using the reference management programme RefWorks (Ann Arbor, MI, USA). Duplicates between the two searches were removed manually. The complete search strategy is provided in the online supplementary material.

Study selection

Title and abstract of the retrieved articles were reviewed and articles were scored based on the following three criteria. Studies involving 1) ILD, mouse models or cells and lung disease; 2) surfactant-processing mutation involved in adult pulmonary fibrosis; and 3) original research articles. Abstracts that were scored for all three criteria were selected and the full-text versions were reviewed. Studies were excluded that reported no or only non-pharmacological drug effects, such as small interfering RNA/short hairpin RNA,

gene overexpression, supplemental oxygen, bronchoalveolar lavages and lung transplantation. Case reports/series were excluded in which HPS diagnosis was not based on genetic analysis or absence of dense granules in platelets assessed by electron microscopy. The references of the finally selected articles were screened for additional eligible studies.

Classification of drug effect in case reports/series

Drug effect in case reports or series of paediatric and adult cases was determined based on the information found in journal articles. Different terms, such as improvement, short-term improvement, stabilisation, short-term stabilisation, limited effect or no effect were used to express outcome of treatment. Sick-better, (some) improvement of lung function, clinical or respiratory symptoms, chest film or high-resolution computed tomography (HRCT) or just improvement after treatment was defined as improvement; transient effect or improvement and later a reduced effect of treatment or deterioration of disease was defined as short-term improvement; stable condition, stabilisation of lung function, clinical symptoms or sick-same was defined as stabilisation. Short-term stabilisation was used when this drug effect was only present for a short period of time. No effect after treatment, deterioration of lung function, clinical symptoms or HRCT was defined as no effect; and limited effect was used when little effect or minimal improvement followed by death was reported.

Results

Search results

In figure 1, the flow diagram of the search and study selection process is displayed. Two different searches, one with three groups of search terms (ILD/lung cells, surfactant-processing mutation and treatment) and one with two groups of search terms (ILD/lung cells and surfactant-processing mutation) were performed. The searches resulted in a total of 1878 unique articles. The full text was read of 239 articles, of which 73 were selected to be included in this review. Selected studies consisted of 16 studies performed in cell or mouse models, 55 case reports/series and two clinical trials. Mutations in *SFTPC*, *HPS1* and *ABCA3* were most frequently studied. The number of case reports/series, clinical trials and cell/mouse studies per mutation are displayed in table 1.

Drugs and effect parameters used in case reports/series and cell/mouse studies

The studied drugs can be divided into immunosuppressive agents, antifibrotic agents, mitogen-activated protein kinase signalling pathway inhibitors, antibiotics, combination therapy, anti-apoptotic therapy and

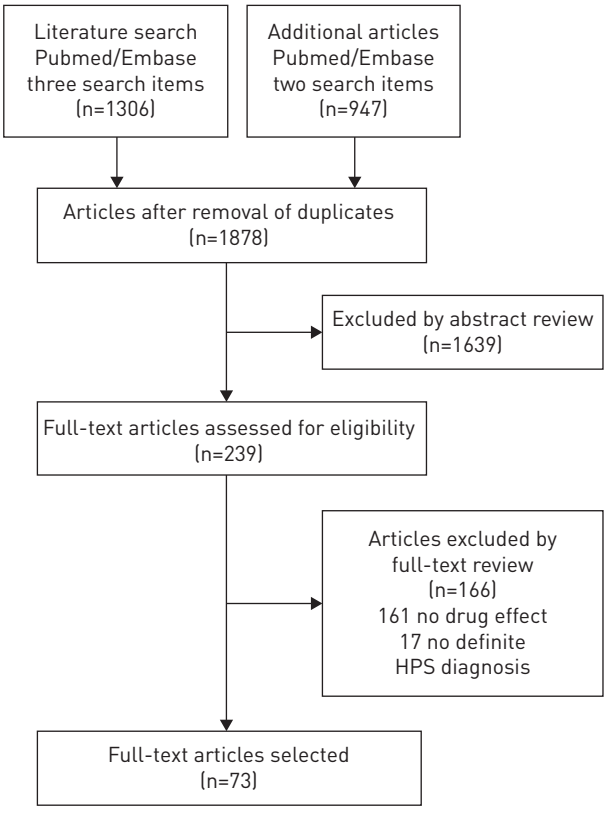

FIGURE 1 Flowchart of the article selection process. HPS: Hermansky–Pudlak syndrome.

TABLE 1 Included studies on surfactant-processing mutations categorised by study type

	Study type					Total n
	Adult case reports/series	Paediatric case reports/series	Adult paediatric case reports/series	Clinical trial	Cell/mouse model	
SFTPA2	1 [7]	0	0	0	1 [35]	2
SFTPC	0	20 [5, 36–54]	1 [55]	0	10 [21, 56–64]	31
ABCA3	0	20 [65–84]	2 [10, 85]	0	1 [86]	23
SFTPC/ABCA3		2 [87, 88]				2
HPS1/2/4	8 [89–96]	1 [13]		2 [97, 98]	4 [99–102]	15
Total	9	43	3	2	16	73

Data are presented as number of studies and their corresponding references.

other therapies. 55 case reports/series were included, of which 43 described paediatric cases, nine described adult cases and three described paediatric as well as adult cases. Adult patients were treated with corticosteroids, cyclosporine A, antibiotics, pirfenidone and/or azathioprine. Additional drugs used in paediatric patients were exogenous surfactant and hydroxychloroquine. Two clinical trials were included in which patients were treated with pirfenidone (table 2). The same drugs were tested in cell and mouse models (table 3). Additionally, drugs tested in cell and mouse models were glycerol, rapamycin, 4-phenylbutyric acid (PBA), saralasin, angiotensin (ANG)1–7, cyclophosphamide, recombinant CHI3L1, interleukin (IL)13Rα2 construct, antibodies against monocyte chemotactic protein (MCP)-1 or SP-D and specific inhibitors for c-Jun N-terminal kinases (JNK), caspase 4, ADAM metallopeptidase domain 17/tumor necrosis factor-α-converting enzyme (ADAM17/TACE), synoviolin and extracellular signal-regulated kinases (ERK1/2, P38, nuclear factor (NF)-κB and CRTH2).

Human studies reported clinical symptoms, lung function, radiological characteristics or oxygen requirement as effect parameters. A majority of the cell-line and mouse studies investigated alterations in processes involved in surfactant trafficking [21, 35, 56–58], cytokine/chemokine concentrations [59, 60, 86, 99] and necrosis/apoptosis [21, 57, 61–63, 100], while some studies investigated weight loss, airway compliance [60], collagen secretion/accumulation [64, 100], migration of macrophages [101] or mortality [102] (table 3 and figure 2).

Outcome in case reports/series and clinical trials

An extensive description of the effect of treatment in paediatric and adult cases with a surfactant-processing mutation is described in online supplementary table S1. A concise outcome after treatment per drug combination (no effect, (short-term) improvement, (short-term) stabilisation, little effect) was determined based on the information derived from case reports/series. In addition, an overall outcome after treatment was determined based on the last reported outcome after treatment with different drugs and displayed in table 2. In six of the 12 adult case studies (five patients in total) [7, 10, 85, 89–91], (short-term) improvement or (short-term) stabilisation of the disease was observed after treatment with pirfenidone, corticosteroids or antibiotics. In paediatric case studies (short-term) stabilisation or (short-term) improvement of disease was observed in 20 of the 23 case reports/series [5, 36–51, 87, 88, 103] (in five case series, not in all described cases; total 67 patients) describing patients with a *SFTPC* mutation treated with hydroxychloroquine, surfactant, antibiotics or corticosteroids. In addition, (short-term) improvement or (short-term) stabilisation of disease was found in 15 of the 24 case reports/series describing paediatric cases [10, 65–76, 85, 88] (in four case series, not in all described cases; 28 patients in total) describing patients with an *ABCA3* mutation treated with the same drugs. In one case report describing a drug effect of corticosteroids in a patient with an *AP3B1* mutation, stabilisation of disease was reported [13]. One of the two clinical trials included in this review [97] reported a positive effect of pirfenidone on lung function of HPS patients with a baseline forced vital capacity (FVC) ⩾50% predicted. The other clinical trial reported no statistically significant difference between pirfenidone and the placebo group [98].

Outcome in mouse studies and cells derived from humans with an HPS1 *mutation*

The effect of drugs on mouse or human lung cells with an *HPS1* mutation was investigated in three studies [99–101]. Treatment of alveolar macrophages from bronchoalveolar lavage (BAL) fluid derived from patients with an *HPS1* mutation with pirfenidone resulted in reduced cytokine/chemokine secretion [99]. In addition, changes in macrophage behaviour were found in experiments with BAL fluid from

TABLE 2 Case reports/series and clinical trials of humans with a surfactant-processing mutation involved in fibrotic interstitial pneumonia

	Diagnosis	Drug	Outcome after treatment per drug combination	Overall outcome after treatment	[Ref.]
Adult case reports and series					
SFTPC p.I73T	Adult with CPFE	Prednisone	No effect	No effect	[55]
SFTPA2 p.G231V	1 adult with hypersensitivity pneumonitis	Prednisone and avoidance of birds	Improvement	1 improvement/ 1 no effect	[7]
	1 adult with pulmonary fibrosis and bronchoalveolar carcinoma	Prednisone	No effect		
ABCA3 p.G964D	Adult with pulmonary fibrosis	Antibiotics Prednisone and azithromycin	No effect Stabilisation	Stabilisation	[10]
ABCA3 p.G964D	Adult with restrictive lung disease	Steroids and azithromycin	(Short-term) improvement	Stabilisation	[85]
HPS#	Adult with HPS	Antibiotics and oxygen inhalation	No effect	No effect	[92]
HPS1 IVS5+5 G>A	Adult with HPS	Prednisolone, cyclosporine A + pirfenidone	No effect Short-term stabilisation	Short-term stabilisation	[91]
HPS4 p.Q620X	Adult with HPS	Corticosteroids, pirfenidone	Stabilisation	Stabilisation	[90]
HPS1 p.L668P	Adult with HPS	Prednisolone, pirfenidone, azathioprine	No effect	No effect	[93]
HPS#	Adult with HPS	Oral corticosteroids	No effect	No effect	[94]
HPS4 p.685delC	Adult with HPS	High-dose steroids and azathioprine	No effect	No effect	[95]
HPS#	Adult with HPS and pulmonary sarcoidosis	Prednisone	Improvement	Improvement	[89]
HPS#	Adult with HPS	Prednisolone and pirfenidone	No effect	No effect	[96]
Paediatric case reports/series with *SFTPC* mutations					
SFTPC p.I73T p.I38F, p.V39L	4 children with DIP, 1 child with chronic interstitial pneumonitis (p.V39L)	1/5 systemic steroids 5/5 hydroxychloroquine	No effect 2 short-term improvement, 3 improvement	2 short-term improvement/3 improvement	[36]
SFTPC p.A116D	Child with NSIP	Hydroxychloroquine and supplemental oxygen	Improvement	Improvement	[37]
SFTPC p.I73T	Child with ILD	Corticosteroids and supplemental oxygen	Improvement	Improvement	[55]
SFTPC c.460+1 G → A	Child with cellular or NSIP	Corticosteroids and supplemental oxygen	Improvement	Improvement	[5]
SFTPC p.I73T	5 children with chronic ILD	5/5 methylprednisolone, 4/5 hydroxychloroquine, 5/5 supplemental oxygen	5 improvement	5 improvement	[38]
Different *SFTPC* BRICHOS/non-BRICHOS	17 children with ILD (NSIP, PAP or DIP)	14/17 hydroxychloroquine 15/17 systemic steroids 7/17 surfactant 3/17 colchicine	12/14 improvement 2/14 no effect 14/15 improvement 1/15 no effect 2/7 improvement, 5/7 no effect 3 no effect	7 improvement/ 7 stabilisation/ 3 no effect	[39]
SFTPC 14 non-BRICHOS, 6 BRICHOS	22 children with chronic ILD at diagnosis	18/22 methylprednisolone, 11/22 hydroxychloroquine, 5/22 azithromycin, 20/22 supplemental oxygen	6/22 no effect, 16/22 improvement	16 improvement/ 6 no effect	[40]

Continued

TABLE 2 Continued

	Diagnosis	Drug	Outcome after treatment per drug combination	Overall outcome after treatment	[Ref.]
SFTPC p.G97S	Child with CPI pattern with globular alveolar proteinosis	Home ventilator support, oxygen, pulse methylprednisolone, azithromycin, hydroxychloroquine	Improvement	Improvement	[41]
SFTPC p.I73T, p.I38F	2 children with CPI	Hydroxychloroquine, prednisone, ranitidine, TMP-SMX; 2 months after therapy began, pulse therapy of methylprednisolone; later, hydroxychloroquine alone	2 improvement	2 improvement	[42]
SFTPC p.I73T	Child with CPI, pneumatoceles after biopsy	Methylprednisolone, hydroxychloroquine, azithromycin	Improvement	Improvement	[43]
SFTPC p.I73T	Child with ILD	Hydroxychloroquine, oxygen supplementation	Improvement	1 improvement/ 1 stabilisation/ 1 no effect	[44]
	Child with ARDS/DIP	Supplemental oxygen and steroids	No effect		
		Steroids pulse therapy	Short-term improvement		
		Hydroxychloroquine	Improvement		
		Hydroxychloroquine replaced by azithromycin	Stabilisation		
	Child with DIP	Hydroxychloroquine and steroids	No effect		
SFTPC p.I73T	Child with chILD	Bronchodilators, inhaled corticosteroids and antileukotrienes, azathioprine, hydroxychloroquine and *i.v.* immunoglobulins, exogenous surfactant	No effect	No effect	[52]
SFTPC p.I73T	Child with PAP and NSIP	Supplemental oxygen, whole-lung lavages, systemic corticosteroids and azathioprine	Short-term improvement	Short-term improvement	[45]
		Additional corticosteroid pulse therapy plus azathioprine	No effect		
SFTPC Δexon 4	Child with respiratory distress	Oral and *i.v.* corticosteroids, hydroxychloroquine, supplemental oxygen	Improvement	Improvement	[51]
SFTPC p.E66K, p.I73T, p.V102M, p.A155P	8 children with idiopathic diffuse lung diseases	2 children supplemental oxygen, pulse steroids and hydroxychloroquine	2 limited effect	2 limited effect/6 stabilisation	[46]
		Supplemental oxygen, pulse steroids, hydroxychloroquine	Stabilisation		
		Supplemental oxygen, hydroxychloroquine	Stabilisation		
		Supplemental oxygen, steroids, hydroxychloroquine, azithromycin	Stabilisation		
		Supplemental oxygen, pulse steroids, hydroxychloroquine	Stabilisation		
		Supplemental oxygen, pulse steroids, bronchodilators, antibiotics	Stabilisation		
		Steroids, supplemental oxygen	Stabilisation		
SFTPC p.L188Q	2 children with respiratory distress (NSIP-like pattern)	Methylprednisolone and hydroxychloroquine	2 no effect	2 no effect	[53]
SFTPC[#]	Child with CPI	Corticosteroids, hydroxychloroquine and continuous oxygen	Short-term improvement	Short-term improvement	[47]

Continued

TABLE 2 Continued

	Diagnosis	Drug	Outcome after treatment per drug combination	Overall outcome after treatment	[Ref.]
SFTPC p.I73T	Child with NSIP/PAP	Supplemental oxygen, antibiotics and oral corticosteroids	No effect	No effect	[54]
SFTPC p.I73T	Child with PAP/ILD	Whole-lung lavages, systemic corticosteroids and azathioprine	Improvement	Improvement	[48]
SFTPC p.G182R, p.L188Q, p.C189W	1 child with PAP/NSIP	Clearance, steroids, hydroxychloroquine, mechanical ventilation	Improvement	3 improvement	[49]
	1 child with respiratory failure	Clearance, steroids, azathioprine, mechanical ventilation	Improvement		
	1 child with respiratory failure	Steroids, azithromycin, hydroxychloroquine, mechanical ventilation	Improvement		
SFTPC p.L81V	Child with surfactant protein C deficiency	Hydroxychloroquine, oxygen therapy	Improvement	Improvement	[87]
SFTPC#	Child with NSIP	Systemic steroids, azathioprine, hydroxychloroquine	Improvement	Improvement	[88]
Different *SFTPC* mutations	15 children with interstitial chronic lung disease	All methylprednisolone 5/15 azithromycin 8/15 hydroxychloroquine	11 no effect/ 4 improvement	11 no effect/ 4 improvement	[50]
Paediatric case reports/series with *ABCA3* mutations					
ABCA3#/*SFTPC*	Child with DPLD/surfactant dysfunction	Surfactant Systemic steroids	Improvement No effect	2 short-term improvement/ 1 no effect	[88]
ABCA3#	Child with CPI	Systemic steroids, surfactant Chloroquine	Improvement No effect		
	Child with DIP	Systemic steroids, hydroxychloroquine	No effect		
ABCA3 c.358_359del	Child with ABCA3 deficiency	Methylprednisolone, oxygen therapy	Limited effect	Limited effect	[87]
ABCA3 p.W1148X and p.T1114A	Child with PAP-like features	Methylprednisolone, antibiotics, antivirals and antifungals, oxygen, mechanical ventilation	No effect	Improvement	[76]
		BAL with bovine surfactant Hydroxychloroquine	Improvement Improvement		
ABCA3 p.G964D	Child with (possible) IPF	Prednisone and macrolides	Improvement	Improvement	[10]
ABCA3 p.A307V	Child with respiratory distress	Dexamethasone and surfactant, CPAP	Short-term improvement	Improvement	[75]
		Methylprednisolone, azithromycin, hydroxychloroquine	Improvement		
ABCA3 p.Y1515X	Child with RDS	Pulse steroids, antibiotics	No effect	No effect	[77]
ABCA3 p.R194G and V1615GfsX15	2 children with IRDS	CPAP, corticosteroids and hydroxychloroquine	2 limited effect	2 limited effect	[78]
ABCA3 p.D253H	Child with DPLD	Methylprednisolone, oral prednisone, oxygen therapy	No effect	Improvement	[74]
		Azithromycin	Improvement		
ABCA3 p.R280C and p.E690G	Child with DIP	Oxygen supplementation, surfactant therapy, corticosteroids	No effect	Improvement	[73]
		Hydroxychloroquine	Improvement		

Continued

TABLE 2 Continued

	Diagnosis	Drug	Outcome after treatment per drug combination	Overall outcome after treatment	[Ref.]
ABCA3 p.D507del CA Ter 508, p.D696N	Child with DIP	Dexamethasone, supplemental oxygen, surfactant therapy Methylprednisolone, azithromycin, hydroxychloroquine	Short-term improvement Improvement	Improvement	[72]
ABCA3 p.K914R, p.L1238_E1239insGG	Child with ILD	Methylprednisolone, antibiotics + hydroxychloroquine	Limited effect Improvement	Improvement	[71]
ABCA3 c.59G>T and c.2646_2647insC	Child with severe RDS	Home ventilator, methylprednisolone, hydroxychloroquine, azithromycin	Improvement	Improvement	[70]
ABCA3 p.H778R, p.L1252P	Child with DIP-like pattern	Methylprednisolone, prednisone and hydroxychloroquine, clarithromycin	Improvement	Improvement	[69]
Different *ABCA3* mutations	9 children with PAP pattern, DIP pattern and NSIP pattern	All corticosteroids, 7/9 hydroxychloroquine	4 no effect, 2 stabilisation, 3 improvement	4 no effect, 2 stabilisation, 3 improvement	[68]
ABCA3, p.L798P, p.R1612P	Child with DIP	Antibiotics, supplemental oxygen, exogenous surfactant, methylprednisolone, hydroxychloroquine	No effect	No effect	[79]
ABCA3 p.R1561Stop	Child with respiratory distress with cyanosis	Antibiotics, surfactant, dexamethasone, inhaled nitric oxide, methylprednisolone, hydroxychloroquine	Short-term improvement	Short-term improvement	[67]
ABCA3 large deletion exon 2–5	Child with IRDS	N-CPAP, surfactant therapy, dexamethasone	No effect	No effect	[80]
ABCA3 ΔF1203 and c.1375ins15	Child with IRDS	Supplemental oxygen and systemic corticosteroids and diuretics	No effect	No effect	[81]
ABCA3 p.R20L and c.4483del25	Child with ILD	Prednisolone and supplemental oxygen	No effect	No effect	[82]
ABCA3 heterozygous p.E292V	Child with cerebropulmonary dysgenetic syndrome	CPAP, mechanical ventilation and antibiotics	No effect	No effect	[84]
ABCA3 p.S1116F	Child with RDS	Supplemental oxygen, mechanical ventilation, exogenous surfactant, antibiotics and inhaled nitric oxide	No effect	No effect	[83]
ABCA3 mutation[#]	19 children (14 RDS, 4 RDS/PAP, 1 PAP)	16/19 surfactant	7 no effect, 9 improvement/short-term improvement	29 no effect/ 3 improvement/ 3 stabilisation	[85]
		19/19 systemic steroids	14 no effect, 5 improvement/short-term improvement		
		9/19 hydroxychloroquine	5 no effect, 4 improvement/short-term improvement		

Continued

TABLE 2 Continued

	Diagnosis	Drug	Outcome after treatment per drug combination	Overall outcome after treatment	[Ref.]
Heterozygous *ABCA3* mutation[#]	16 children (9 with RDS, 4 with RDS/PAP, 1 PAP, 2 chILD)	2/19 azithromycin	2 no effect		
		12/16 surfactant	8 no effect, 4 improvement/short term improvement		
		12/16 systemic steroids	8 no effect, 4 improvement/ short-term improvement		
		8/16 hydroxychloroquine	3 no effect, 5 improvement/ short-term improvement		
ABCA3 p.M1227R and Ins1510fs/ter1519	Child with DIP	Macrolides, dexamethasone, mechanical ventilation	No effect	Short-term improvement	[66]
		Surfactant	Short-term improvement		
ABCA3 heterozygous R288K (7 patients) p.R43L, R288K + c.4751delT (1 patient), R288K, P766S (heterozygous, 1 patient), R288K, S693L (heterozygous, 1 patient), R288K, Q215K (1 patient)	11 children with ILD	5/11 prednisolone, surfactant, oxygen or corticosteroids	No effect	5 no effect/ 6 improvement	[65]
		6/11 oxygen, aspirin, surfactant, dexamethasone, montelukast, salbutamol, steroids, hydroxychloroquine, azathioprine, azithromycin or antibiotics	Improvement		
Paediatric case report with *AP3B1* mutation					
AP3B1 p.R509X and p.E659X	Child with HPS2	Oxygen, systemic corticosteroids, G-CSF	Stabilisation	Stabilisation	[13]
Clinical trials					
HPS1[¶]	21 adults with HPS	11 treated with pirfenidone, 10 placebo	Pirfenidone superior to placebo: ΔFVC of 0.46% per month (p=0.587) Restricted group including only patients with initial FVC values >50% pred: difference in pulmonary function ~0.7% per month (p=0.02)		[97]
HPS1 or 4[+]	35 adults with HPS	23 treated with pirfenidone, 12 placebo	No statistically significant difference in lung function		[98]

ABCA3 mutations were compound heterozygous or homozygous mutations, unless otherwise stated. CPFE: combined pulmonary fibrosis and emphysema; HPS: Hermansky–Pudlak syndrome; DIP: desquamative interstitial pneumonia; NSIP: nonspecific interstitial pneumonia; ILD: interstitial lung disease; PAP: pulmonary alveolar proteinosis; CPI: chronic pneumonitis of infancy; ARDS: acute respiratory distress syndrome; chILD: childhood ILD; DPLD: diffuse parenchymal lung disease; BAL: bronchoalveolar lavage; IPF: interstitial pulmonary fibrosis; (N)-CPAP: (nasal)-continuous positive airway pressure; RDS: respiratory distress syndrome; IRDS: infant respiratory distress syndrome; G-CSF: granulocyte colony-stimulating factor; ΔFVC: change in forced vital capacity. [#]: specific mutation not mentioned in the article, diagnosis based on absence of platelet dense bodies under electron microscopy or genetic testing; [¶]: 20 of these patients were Puerto Ricans homozygous for a 16-bp duplication in exon 15 of the *HPS1* gene, which leads to a frameshift. The other patient was a Puerto Rican with a 3904-bp deletion in the *HPS3* gene; [+]: 33 of these patients were Puerto Ricans homozygous for the known 16-bp duplication in exon 15 of the HPS1 gene. Two patients were non-Puerto Rican, and the mutations in these patients are not reported.

TABLE 3 Drug effect in cell and mouse models with a surfactant-processing mutation

	Effect parameter	Outcome after treatment	Model system	Gene mutation	[Ref.]
Immunosuppressive agents					
Azathioprine	Chaperone protein expression	Calnexin, calreticulin, HSP70: no effect[#] HSP90: increased[#]	MLE12	*SFTPC* p.A116D, p.I73T	[21, 57]
	LDH release	Further increased	MLE12	*SFTPC* p.A116D	[57]
		Increased		*SFTPC* p.I73T	[21]
(Hydroxy)chloroquine	Accumulation SP-C proprotein	Increased	MLE12, HEK293	*SFTPC* p.L188Q	[56]
		No significant effect	HEK293	*SFTPC* p.I73T, Δexon4	
	SP-C mature protein	No significant effect	HEK293	*SFTPC* p.L188Q, p.I73T, Δexon4	
		No significant effect	MLE12	*SFTPC* p.L188Q	
	Mislocalisation defect proSP-C	No significant change	MLE12	SFTPC p.I73T	[21]
	Chaperone protein[#]	Calnexin: no effect Calreticulin, HSP90: increased	MLE12	*SFTPC* p.A116D p.I73T	[21, 57]
	HSP70 protein expression[#]	Increased		*SFTPC* p.A116D	[57]
		No effect		*SFTPC* p.I73T	[21]
	LDH release	No effect on increased levels	MLE12	*SFTPC* p.A116D	[57]
		Increased		*SFTPC* p.I73T	[21]
	LPC and PC levels	Intracellular: no correction loss of PC, amelioration of LPC increase Supernatant: amelioration of the reduction in PC, but no significant effect on increased LPC	MLE12	*SFTPC* p.I73T	[21]
		Intracellular: amelioration of reduced PC, reduction in increased LPC Supernatant: no effect on PC, restored LPC		*SFTPC* p.A116D	[57]
Methylprednisolone	Chaperone protein expression[#]	Calnexin, calreticulin: no effect HSP90 increased	MLE12	*SFTPC* p.A116D, p.I73T	[21, 57]
	HSP70 protein expression[#]	Increased		*SFTPC* p.A116D	[57]
		No effect		*SFTPC* p.I73T	[21]
	LDH release	No effect	MLE12	*SFTPC* p.A116D, *SFTPC* p.I73T	[21, 57]
	Mislocalisation defect proSP-C	Partial correction of reduced proSP-C in secretory vesicles and increased proSP-C in early endosomal vesicles	MLE12	*SFTPC* p.I73T	[21]
	PC and LPC levels	Intracellular: no correction of loss of PC, amelioration of increased LPC Supernatant: no effect on PC and no effect on increased LPC	MLE12	*SFTPC* p.A116D	[57]
		Intracellular: no correction loss of PC, amelioration of LPC increase Supernatant: amelioration of the reduction in PC, but no significant effect on increased LPC		*SFTPC* p.I73T	[21]
Cyclophosphamide	Chaperone protein expression[#]	Calnexin: no effect[#] Calreticulin, HSP70, HSP90: increased[#]	MLE12	*SFTPC* p.A116D, p.I73T	[21, 57]
	LDH release	No effect on increased levels		*SFTPC* p.A116D	[57]
		No effect		*SFTPC* p.I73T	[21]

Continued

TABLE 3 Continued

	Effect parameter	Outcome after treatment	Model system	Gene mutation	[Ref.]
Rapamycin	Airway compliance, weight loss	Further reduced	129S6/Sv Bleomycin-treated mice	*SFTPC*-/-	[60]
	IL-4, IL-13 gene expression	Further increased			
	Total lung collagen, IFN-γ gene expression, airway resistance	No effect on increased levels			
	Total BALF cells	Attenuation of increase			
Ascorbate or anti-SP-D and/or anti-MCP-1	Migration of RAW 264.7 cells	Amelioration of increase	BAL from EPPE C57BL/6J mice and HPS1 patients	*HPS1*	[101]
4-phenylbutyric acid	Accumulation of detergent insoluble aggregates	Further increased	HEK293	*SFTPC* p.L188Q	[56]
		No change in increase		*SFTPC* p.I73T	
		Slightly increased		*SFTPC* Δexon4	
		NP-40 insoluble aggregates: slight attenuation of increase	CHO-K1	*SFTPA2* p.G231V	[35]
		NP-40 insoluble aggregates: amelioration of increase		*SFTPA2* p.F198S	
	Accumulation of SP-C proprotein	No significant change in increase	HEK 293	*SFTPC* p.I73T	[56]
		Attenuation of reduction		*SFTPC* p.L188Q, Δexon4	
	Juxtanuclear mutant SP-C accumulation	Corrected	A549	*SFTPC* Δexon4	[58]
	SP-C mature protein	Increased to WT concentrations	HEK293	*SFTPC* p.L188Q	[56]
		Amelioration of reduction		*SFTPC* p.I73T	
		No effect on reduced expression		*SFTPC* Δexon4	
	Mutant SP-A2 protein secretion	Partial attenuation of reduction	CHO-K1	*SFTPA2* p.G231, p.F198S	[35]
	ER stress	Increased	HEK293	*SFTPC* p.L188Q	[56]
		No effect		*SFTPC* Δexon4 and p.I73T	
	ER stress-induced factors (spliced XBP1, ATF6, cathepsin D)	Attenuation of increase	A549	*SFTPC* p.G100S	[63]
	Phosphorylation of eIF2α	Attenuation of increase	A549	*SFTPC* p.G100S	
	Caspase 3 activation	Attenuation of increase	A549	*SFTPC* p.G100S	
	Nuclear fragmentation	Attenuation of increase	A549	*SFTPC* p.G100S	
	ADAM17/TACE levels	Attenuation of increase	A549	*SFTPC* p.G100S	
	NF-κB induction	Amelioration of increase	A549	*SFTPC* Δexon4	[59]
	Phosphorylated JNK and AP-1 expression	Hardly any change in increased expression	A549	*SFTPC* Δexon4, p.L188Q	
		Stimulated	HEK293		
	IL-8 concentration	Enhanced	A549	*SFTPC* Δexon4	
Anti-fibrotic/ immunosuppressive agent					
Pirfenidone	GM-CSF and IL-12p40 expression	No effect on increased levels,	Alveolar macrophages from BALF of HPS1 subjects	*HPS1*	[99]
	MIP-1α, MCP-1, RANTES, M-CSF, MIP-4 and IFN-γ	Amelioration of increase			

Continued

TABLE 3 Continued

	Effect parameter	Outcome after treatment	Model system	Gene mutation	[Ref.]
MAPK signalling pathway inhibitors					
ERK 1/2 inhibitor	IL-8 secretion	Attenuation of increase	A549	ABCA3 p.T1173R	[86]
P38 inhibitor	IL-8 secretion	No effect	A549	ABCA3 p.T1173R	[86]
SP600125 (JNK inhibitor)	IL-8 concentration	Completely inhibited the increase in concentration	A549	*SFTPC* Δexon4	[59]
		No effect	A549	ABCA3 p.T1173R	[86]
Antibiotics					
Bafilomycin A1/azithromycin	Accumulation SP-C proprotein	No significant effect	HEK293	*SFTPC* p.I73T, Δexon4	[56]
		Increased	MLE12, HEK293	*SFTPC* p.L188Q	
	SP-C mature protein	No significant effect	HEK293	*SFTPC* p.L188Q, p.I73T, Δexon4	
		No significant effect	MLE12	*SFTPC* p.L188Q	
Combination therapy					
4-phenylbutyric acid + SP600125 (JNK inhibitor)	IL-8 concentration	Completely antagonised	A549	*SFTPC* Δexon4	[59]
SP600125 (JNK inhibitor) and/or caspase 4 inhibitor	Activation of caspase 3 cleavage	Amelioration of increase	HEK293	*SFTPC* Δexon4, p.L188Q	[61]
	DNA fragmentation		HEK293/A549	*SFTPC* Δexon4	
Anti-apoptotic therapy					
Pan-caspase inhibitor	Mortality	Amelioration of increase	Bleomycin challenged C57BL/6J mice	*HPS2* homozygous	[102]
Other drugs					
TAPI-2 (ADAM17/TACE-specific inhibitor)	ACE-2 loss	Amelioration of increase	A549	*SFTPC* p.G100S	[62]
Saralasin (ANGII receptor antagonist), synthetic ANG1–7	Increase in nuclear fragmentation[#]	Reduced to WT levels	A549	*SFTPC* p.G100S	[62]
Glycerol	SP-C concentration	Unchanged	HEK293	*SFTPC* p.L188Q, Δexon4, p.I73T	[56]
LS-102 (synoviolin inhibitor)	Collagen secretion	Attenuation of increase	A549	*SFTPC* Δexon4	[64]
NF-κB inhibitor	IL-8 secretion	No effect	A549	ABCA3 p.T1173R	[86]
Recombinant CHI3L1	Cell apoptosis	No effect	Bleomycin-treated AEC2 from pale ear C57BL/6 mice	*HPS1* null	[100]
IL-13Rα2 construct	Cell apoptosis	Amelioration of increase	Bleomycin-treated AEC2 from pale ear C57BL/6 mice	*HPS1*	[100]
CRTH2 inhibitor	Collagen accumulation	Amelioration of increase	Bleomycin-treated AEC2 from pale ear C57BL/6 mice	*HPS1*	[100]

SP: surfactant protein; MCP: monocyte chemotactic protein; MAPK: mitogen-activated protein kinase; ERK: extracellular signal-regulated kinase; JNK: c-jun N-terminal kinase; ANG: angiotensin; NF: nuclear factor; IL: interleukin; HSP: heat shock protein; LDH: lactate dehydrogenase; LPC: lysophosphatidylcholine; PC: phosphatidylcholine; IFN: interferon; BAL: bronchoalveolar lavage; EPPE: Hps1ep/Hps1ep, Ap3b1pe/Ap3b1pe; BALF: bronchoalveolar lavage fluid; WT: wild type; ER: endoplasmic reticulum; GM-CSF: granulocyte-macrophage colony stimulating factor; MIP: macrophage inflammatory protein; ACE: angiotensin-converting enzyme; AEC2: alveolar type II cells. [#]: outcome compared to untreated wild type.

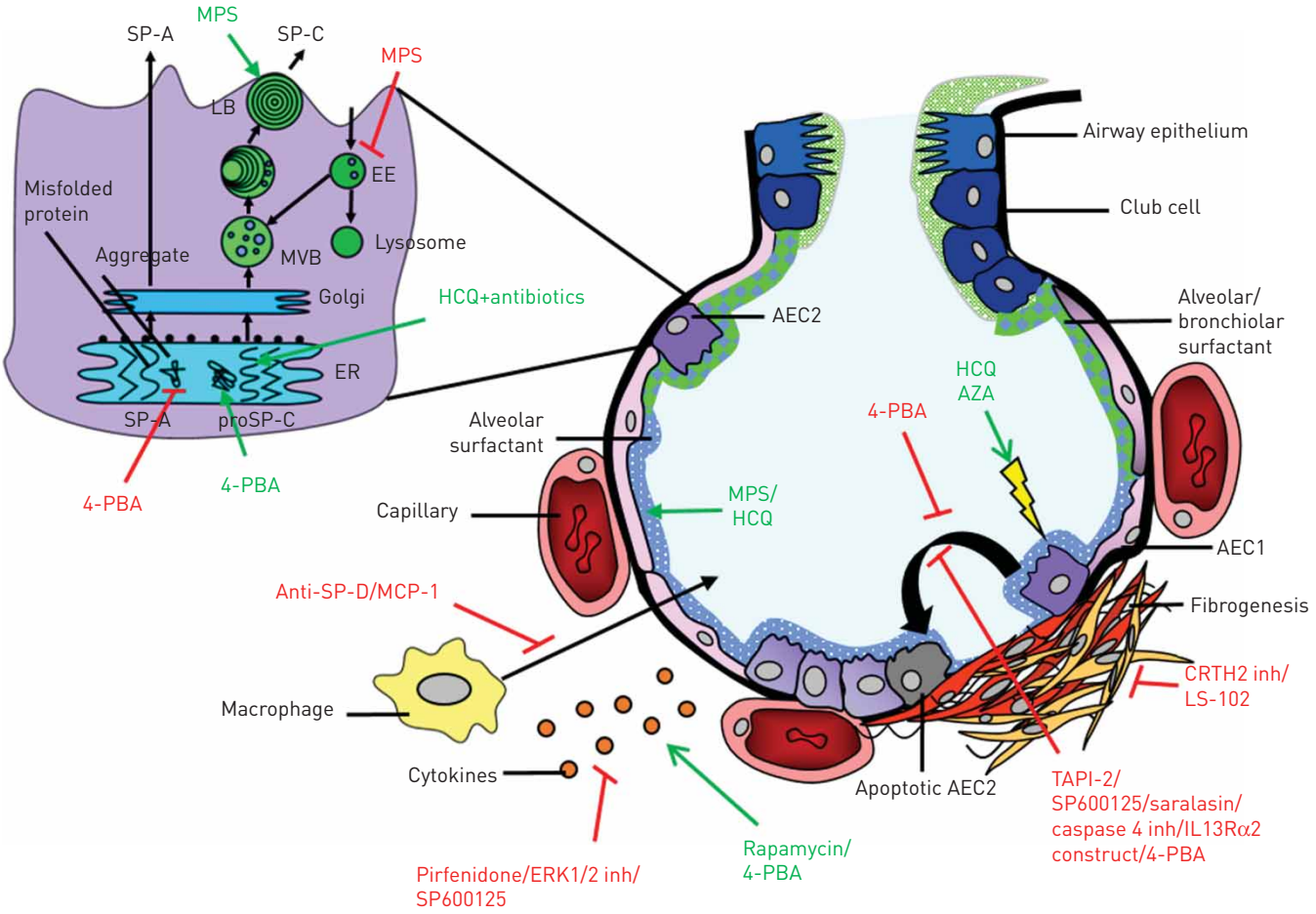

FIGURE 2 Targets of drugs investigated in humans and disease models with a surfactant-processing mutation. Damage to alveolar tissue causes fibrogenesis, which can be targeted by drugs in multiple ways. Expanded section: alveolar type II cell (AEC2) with organelles involved in surfactant processing. MPS: methylprednisolone; SP: surfactant protein; LB: lamellar bodies; EE: early endosomes; MVB: multivesicular bodies; ER: endoplasmic reticulum; 4-PBA: 4-phenylbutyric acid; MCP: monocyte chemotactic protein; ERK: extracellular signal-regulated kinases; HCQ: hydroxychloroquine; AZA: azathioprine; AEC1: alveolar type I cell; inh: inhibitor.

patients with an *HPS1* mutation and Hps1ep/Hps1ep, Ap3b1pe/Ap3b1pe (EPPE) C57BL/6J mice treated with anti-MCP1 and/or anti-SP-D. This resulted in reduced macrophage migration [101]. In addition, bleomycin-treated *HPS1* mutated mouse AEC2 were treated with CHI3L1, IL13Rα2 and CRTH2, which resulted in no effect on apoptosis, amelioration of apoptosis and reduced collagen accumulation, respectively [100].

Outcome in cell lines with a pulmonary surfactant associated mutation

The most frequently studied drugs in cell lines with a surfactant-processing mutation are 4-phenylbutyric acid (n=5), JNK inhibitor (n=3), hydroxychloroquine (n=3), methylprednisolone (n=2), azathioprine (n=2) and cyclophosphamide (n=2). Hydroxychloroquine or methylprednisolone treatment was found to have a positive effect on lysophosphatidylcholine and phosphatidylcholine levels in MLE12 cells transfected with *SFTPC*^{I73T} [21] or *SFTPC*^{A116D} [57]. In addition, treatment with methylprednisolone, but not hydroxychloroquine, resulted in partial correction of the mislocalisation of pro-SP-C in MLE12 cells expressing SP-C^{I73T} [21]. Furthermore, another study with MLE12 cells expressing SP-C^{L188Q} treatment with hydroxychloroquine resulted in increased accumulation of pro-SP-C [56]. Azathioprine seems to have a negative effect on MLE12 cells transfected with *SFTPC*^{I73T} or *SFTPC*^{A116D}, as evidenced by increased LDH levels after treatment. For cyclophosphamide treatment only an effect on chaperone protein expression of heat shock protein (HSP)70 and HSP90 could be found [21, 57].

In A549 cells transfected with *SFTPC*$^{\Delta exon4}$, it was found that 4-PBA attenuated increased NF-κB expression, which is a marker for cellular stress response. However, it had no inhibitory effect on pro-inflammatory interleukin (IL)-8 production [59]. In addition, 4-PBA resulted in reduced NP-40 insoluble aggregate formation and increased protein secretion of SP-A2^{G231V} and SP-A2^{F198S} expressing

CHO-K1 cells [35] and on juxtanuclear accumulation of pro-SPC in *SFTPC*$^{\Delta exon4}$-mutated A549 cells [58]. In contrast, 4-PBA resulted in a slightly increased accumulation of SP-C$^{\Delta exon4}$ and SP-C^{L188Q} proprotein in transfected HEK293 cells. Furthermore, treatment of HEK293 cells transfected with *SFTPC*^{L188Q} with 4-PBA increased endoplasmic reticulum stress and accumulation of detergent insoluble aggregates, but it also resulted in increased mature SP-C^{I73T} and SP-C^{L188Q} protein [56]. In contrast, NGUYEN and UHAL [63] showed that treatment of A549 cells transfected with *SFTPC*^{G100S} with 4-PBA resulted in attenuation of increased endoplasmic reticulum stress-induced factors. This study also showed that treatment with 4-PBA can result in reduced nuclear fragmentation.

Another frequently studied drug in cell models is the JNK inhibitor SP600125, sometimes in combination with 4-PBA or a caspase-4 inhibitor. In A549 cells transfected with *SFTPC*$^{\Delta exon4}$, this drug resulted in reduced IL-8 concentration [59] and DNA fragmentation [61], although it had no effect on IL-8 concentration in A549 cells transfected with *ABCA3*^{T1173R} [86]. Other drugs not currently used in ILD, *e.g.* synoviolin inhibitor and saralasin were tested in cell lines with a surfactant-processing mutation by assessing collagen secretion and endoplasmic reticulum-stress induced processes such as apoptosis or expression of chemokines and cytokines. These drugs were only tested in one study, and yielded both positive and negative results.

Discussion

This systematic review provides an overview of studies that investigated the effect of drugs on patients with ILD and a surfactant-processing mutation or cell or mouse models with a surfactant-processing mutation involved in pulmonary fibrosis. Human studies reported only treatment with antibiotics and drugs against inflammatory or fibrotic processes and evaluated lung function and radiological characteristics over time. Although some positive results were reported in adult case reports/series, except for one case report [10] no curative or long-term stabilising effects on pulmonary fibrosis were reported. In more than half of the case reports/series of children, stabilisation or improvement of disease after treatment was reported. Cell and mouse studies used drugs that interfered with aberrant biological processes related to surfactant mutations. This heterogeneous group of studies showed that results are gene- and mutation-dependent and yielded results that may contribute to the development of personalised medicine in the future.

In two cell line studies with *SFTPC*^{I73T}- and *SFTPC*^{A116D}-mutated cells, addition of methylprednisolone showed the most promising results as it partially corrected mislocalisation of SFTPC and (partially) corrected altered (lyso)phospholipid levels [21, 57]. In addition, glucocorticosteroids have been used for the treatment of patients; in three adult cases [7, 10, 89] with a surfactant-processing mutation, improvement or minimal progression of disease was observed after treatment with prednisone. Two of these patients had diseases that are known to often respond to immunosuppressive therapy. One had concomitant pulmonary sarcoidosis [89] and one had hypersensitivity pneumonitis [7]. Two other adult cases [90, 91] treated with corticosteroids and pirfenidone showed (short-term) stabilisation of the disease. In paediatric cases described in case reports/series included in this review, treatment with antibiotics, hydroxychloroquine or corticosteroids resulted more often in (short-term) improvement or (short-term) stabilisation of disease compared to adult cases. The difference in response may be due to the difference in clinical phenotype between adult and paediatric patients with surfactant-processing mutations. Children commonly present with desquamative interstitial pneumonia, non-specific interstitial pneumonia, pulmonary alveolar proteinosis, chronic pneumonitis of infancy or respiratory distress syndrome, but seldom with IPF. In addition, host environment, initial injury and regenerative capacity of tissue [104] may differ between adults and children.

It is difficult to draw conclusions only based on case reports/series, since the clinical parameters reported are limited and the information is often not quantitative. In addition, only interesting cases are selected for a case report, introducing bias into the results. Griese and colleagues have initiated a trial to investigate the effect of hydroxychloroquine in paediatric ILD in a more standardised way (ClinicalTrials.gov identifier NCT02615938). A significant subgroup of the patients is expected to carry surfactant-processing mutations; therefore, the results of this trial will provide evidence for therapeutic intervention in paediatric patients with these mutations. However, based on the difference between paediatric and adult patients carrying similar surfactant-processing mutations, translation of these results to clinical management of adult patients will need to proceed with utmost care. In addition, immunosuppressive treatment of adult patients with FIP was shown to be unfavourable in patients with IPF. A negative effect on survival and hospitalisation was found in IPF patients receiving the combination treatment of prednisone, azathioprine and N-acetylcysteine in the PANTHER-IPF trial [105] and recently the negative effect of glucocorticoid treatment was reported for a retrospective cohort of suspected IPF patients [106].

Most reports on patients with a surfactant-processing mutation show that disease progresses as monitored by change deterioration of FVC. Clinical trials were only conducted in HPS patients. In two clinical trials

the drug pirfenidone was tested. One trial described a positive effect of pirfenidone on slowing down lung function decrease [97], whereas the other clinical trial found no statistically significant difference between the placebo and pirfenidone group [98]. The placebo group of the last clinical trial showed a small rate of decline in FVC. The positive result of the first trial was closely comparable to that reported by King *et al.* [107] who showed that pirfenidone is effective in slowing down FVC decrease in a cohort of IPF patients (with unknown genetic characteristics) with a baseline FVC ⩾50% predicted. The results of both trials included in this review do not provide unambiguous evidence on whether pirfenidone would be helpful for FIP patients with *HPS* mutations.

In model systems drugs were tested that intervened with the aberrant processes directly related to the surfactant-processing mutation, such as surfactant trafficking, cytokine/chemokine expression, necrosis and apoptosis. The most frequently studied drug in the cell and mouse model studies included in this review is 4-PBA. 4-PBA, a hydrophobic chemical chaperone with a role in promoting trafficking of misfolded proteins, has been approved by the United States Food and Drug Administration for treatment of urea cycle disorders. In addition, its therapeutic effects on other pathologies, such as neurological diseases, diabetes type 2 and protein folding diseases are now being investigated (reviewed by Kolb *et al.* [108]). For 4-PBA a positive effect, and, with other mutations, a negative effect on aggregate formation [35, 56], accumulation of SP-C [56, 58] and SP-C mature protein expression [35, 56] in different SP-A2- and SP-C-mutated cells has been described. In addition, one study has shown that 4-PBA treatment can reduce nuclear fragmentation in $SFTPC^{G100S}$ lung cells [63]. Therefore, further studies are needed to provide evidence for a possible role of 4-PBA in the treatment of patients with surfactant-processing mutations. Other agents, inhibitors against synoviolin, CRTH2, JNK and ANGII receptors showed interesting results in cell studies with a surfactant-processing mutation by reducing collagen secretion/accumulation or nuclear fragmentation. However, future studies, such as replication of cell studies and research in mouse models, including monitoring of side-effects, are still needed.

The investigation of drugs for patients with a *SFTPC* mutation is complicated by the fact that each pro-SP-C mutation seems to result in unique effects on intracellular trafficking of pro-SP-C and the presence of the mature form of SP-C. Even between mutations that are in the same functional domain of the protein (BRICHOS domain) different effects on SP-C processing have been observed [109]. For example, HEK293 cells transfected with $SFTPC^{I73T}$ showed increased accumulation of pro-SPC compared to wild-type, whereas $SFTPC^{L188Q}$ and $SFTPC^{\Delta exon4}$ showed reduced accumulation of pro-SPC [56].

In summary, different drugs have been tested in different cell lines with a surfactant-processing mutation using different outcome measures. Many of these experiments have only been performed once. To investigate the effect of surfactant-processing mutations and the effect of drugs, the development of a new model for IIPs that better represents affected human lungs is highly wanted. In future, lung organoids, *in vitro* three-dimensional lung cell models, may fill the gap between cell lines and humans. Tracheobronchial organoids [110] have already been generated from human tissue explants or biopsies. Stable distal lung organoids, which would be necessary to model surfactant processing adequately, have only been generated from tissue derived from mice [111, 112]. Previously generated distal lung organoids from human lung had a low viability [113], no turnover [114] or high transdifferentiation to type I alveolar epithelial cells [115]. Interestingly, in organoids generated from human-induced pluripotent stem (iPS) cells, alveolar structures have been observed [116, 117]. However, it must be remembered that iPS cells retain characteristics of their cell of origin [118], which might influence their drug response.

In conclusion, this review shows promising drugs described in case reports/series, clinical trials and disease models. One of the two trials in patients with HPS show that patients with surfactant-processing mutations might benefit from anti-fibrotic drugs. Cell and mouse models show that interference with mutation-dependent aberrant processes yield positive results. However, the results seem to be highly gene- and mutation-specific. Translation of these results into personalised medicine is not possible at present. Hopefully, the development of new disease model systems with appropriate outcome parameters will make it possible to test drugs on human lung cells with a specific introduced or native surfactant-processing mutation [119], leading to improved treatment strategies for patients with FIP.

Conflict of interest: None declared.

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