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

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Background

Idiopathic interstitial pneumonias (IIP) are a rare group of diseases characterized by distortion of lung interstitium. A part of IIP patients contains a mutation in a surfactant-processing gene such as, surfactant protein C/A1/A2 (SFTPC/A1/A2), ATP Binding Cassette transporter (ABCA3) or Hermansky-Pudlak sundrome (HPS1/2/4). It is still unknown what type of treatment would be most effective in pulmonary fibrosis patients with surfactant-processing mutations.

Aim: providing 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.

Methods

The electronic databases, Pubmed and EMBASE, were searched for abstracts that included interstitial lung disease, surfactant-processing mutation and treatment. Original research articles that included all three criteria and described a drug effect were included in this review.

Results

Searches in the two electronic databases yielded 1878 unique articles, of which 239 abstracts contained a surfactant-processsing mutation and interstitial lung disease. Drug effect was described in 73 of 239 full text articles. These 73 articles were included in this review. Drug effects were mostly investigated in patients or disease models with a SFTPC or ABCA3 mutation (Table 1). The most frequently used cell lines were A549, MLE12 and HEK293.

Table 1: Number of included studies on surfactant-processing mutations categorized by study type

Mutation	Study type					Total
	Case report/series			Clinical trial	Cell/ mouse model	
	Adult	Paediatric	Adult/ paediatric			
SFTPA2	1	0	0	0	1	2
SFTPC	0	20	1	0	10	31
ABCA3	0	20	2	0	1	23
SFTPC/ABCA3	0	2	0	0	0	2
HPS1/2/4	8	1	0	2	4	15
Total	9	43	3	2	16	73

Drug effects in adult/paediatric cases with a surfactant processing mutation was assessed by lung function, radiological parameters and clinical symptoms. (Short-term) improvement or stabilization of disease was observed after treatment with immuno-suppressive drugs and antibiotics (Table 2).

Table 2: Drug effects in adult and paediatric cases with a surfactant processing mutation

Drugs	Study type					
	Adult cases		Paediatric cases		Clinical trial	
	Positive effect	No effect	Positive effect	No effect	Positive effect	No effect
Steroids	5	6	61	52	n/a	n/a
Hydroxychloroquine	n/a	n/a	61	21	n/a	n/a
Antibiotics	1	2	18	10	n/a	n/a
Azathioprine	n/a	2	9	2	n/a	n/a
Pirfenidone	2	2	n/a	n/a	6	23
Surfactant	n/a	n/a	28	30	n/a	n/a

Positive effect means (short-term) improvement or stabilization. Studies without specification of drug effect per case and drug were not included in this table. Clincical trial s were only performed in patients with an HPS mutation.

Main processes investigated in cell/mouse models with a surfactant-processing mutation were surfactant trafficking, cytokine/chemokine concentrations and necrosis/apoptosis (Figure 1). Promising results were found for 4-phenylbutyric acid (4-PBA), hydroxychloroquine (HCQ) and methylprednisolone (MPS) investigated in multiple studies. However, differences in treatment outcome between different surfactant-processing mutations were observed.

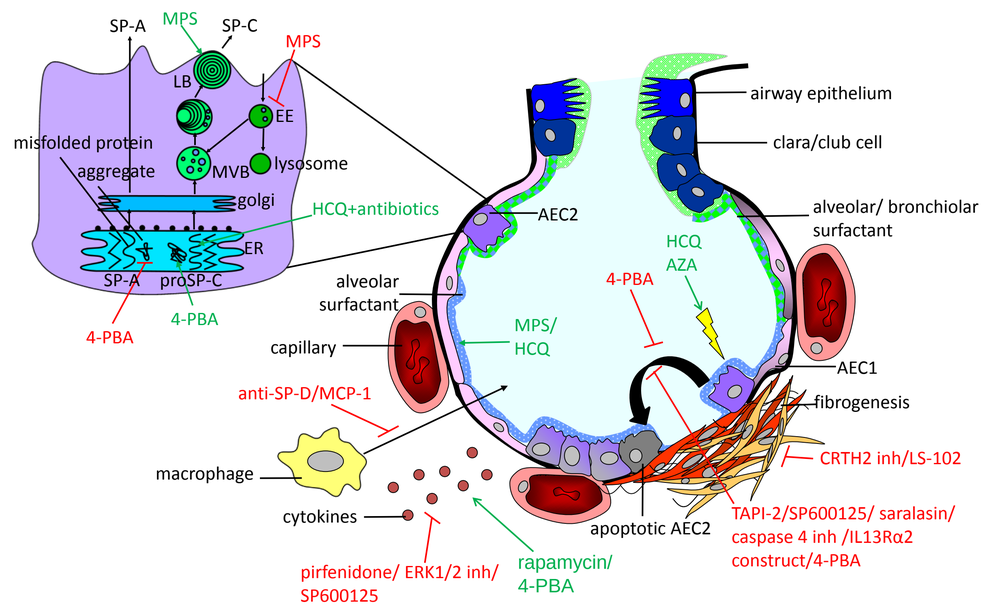

Figure 1: Targets of drugs investigated in humans and disease models with a surfactant-processing mutation
Top left, alveolar epithelial type II cell (AEC2) with organelles involved in surfactant processing
AZA: azathioprine; inh: inhibitor; ER: endoplasmic reticulum; LB: lamellar bodies; MVB: multivesicular bodies; EE: early endosomes; SP-C: surfactant protein C; SP-A: surfactant protein A; SP600125: c-jun N-terminal kinase (JNK) inhibitor; LS-102: Synoviolin inhibitor; TAPI-2: ADAM17/TACE-specific inhibitor; saralasin: ANGII receptor antagonist

Conclusion

- Hydroxychloroquine, methylprednisolone and 4-phenylbutyric acid seem to be most effective in (paediatric) cases and/or disease models with a surfactant-processing mutation
- Treatment outcome is highly gene and mutation dependent
- Further research in improved disease models and patients is needed.

Nederlandse samenvatting

We hebben in de literatuur gezocht naar wat er al bekend is over het effect van medicijnen op patiënten, cellijnen en muismodellen met een verandering in een surfactant-verwerkingsgen gevonden in longfibrose, een ziekte gekenmerkt door littekenweefselvorming in de longen. Immunosuppressiva (hydroxychloroquine en methylprednisolone) en natriumfenylbutyraat (alleen in ziektemodellen) laten de meest veelbelovende resultaten zien. Al zijn er wel verschillen in medicatie effecten gevonden tussen patiënten en ziektemodellen met verschillende genetische veranderingen. Verder onderzoek naar de effecten van medicatie in ziektemodellen en patiënten met een verandering in een surfactant-verwerkingsgen is nodig.

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