Übersichten

Bronchoalveolar Lavage Proteins*

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Summary. Since the discovery of the extra-cellular lining material of the lung and the possibility harvesting this source by endobronchial lavage this material has been the object of many studies directed to analyze its components, function and possible change in the diseased lung.

The best known component of the extra-cellular lining material is the phospholipid and its fatty acid composition. But also on the cellular material much emphasis has been taken with the aim using its cytology as diagnostic parameter. However, very few informations were obtained about the protein material also washed out during the endobronchial lavage.

As it was demonstrated by immunological methods the proteins of the extra-cellular lining material consist of serum identical proteins and those being obviously specific for the lung tissue. As found, most serum identical proteins occure in the same amounts as found in the blood serum, and the molecular weight in general range up to 160,000 daltons indicating that there must be a restriction in passage of high molecular weight proteins through the lumen walls of the endothelium. Some proteins, IgG, IgA, do occure in a higher level in the extra-cellular lining material leading to the suggestion that these proteins were synthesized and secreted by the lung tissue itself. – The molecular weight of the lung specific proteins range from 16,000–340,000 daltons. Under reducing conditions however, for all species listed, two classes of subunits –36,000 and 12,000 daltons – result, indicating that these proteins might have comparable functions in the different species. The exact function of these specific proteins as well as the serum identical proteins till now is not known. One can only speculate that the serum identical proteins will have the same function in plasma and the lung, and that the specific proteins are involved in the formation in the surfactant system. Different amounts of lung specific proteins in lavage of disease lungs suggest that their estimation might be an additional useful parameter in diagnosis of lung diseases.

Key words: Bronchoalveolar lavage – Extra-cellular lining material – Serum identical proteins – Lung specific proteins

The cellular lining of the lung alveoli covering the epithelium of the alveoli and the terminal bronchi is lined with a highly surface-active material, the "pulmonary surfactant" which was first discovered by von Neergaard [65]. This material, known to prevent lung collaps during exspiration [58] could be washed out from the lungs by endobronchial lavage, and has been the object of many studies directed to analyze the components, their function and their possible change in the diseased lung [16, 19, 20, 23, 30, 31, 42, 43, 60, 61, 68].

The clinical importance of surfactant was demonstrated in the end fifties [1, 2, 29] by observations that infants, died from the respiratory distress syndrome, were deficient in surfactant. – Also in animal experiments an altered function of surfactant was reported [33, 35, 36, 55, 79]. On the other hand, in animal and human experiments after synthetic surfactant replacement therapy the surfactant function had been restored [57, 63, 74].

The surfactant is composed of phospholipid and protein components, perhaps acting in molecular interactions. This interaction, however, is not

Abbreviation: ARDS = adult respiratory distress syndrome

well understood, although it is known that at last some of the proteins have the quality of apoproteins perhaps similar to those of the serum.

The best known component of the surfactant system is the phospholipid, the individual phospholipid composition as well as the fatty acid composition [4, 17, 22, 26, 27, 45, 75]. – Also on the cellular material much emphasis has been taken with the aim using its cytology as diagnostic parameter [34, 54].

However, very little informations were obtained about proteins, also washed out by endobronchial lavage. This is astonishing the more since 20–30% by weight, varying from species to species, of the surfactant is protein material. Since in the last decade several studies were done on proteins, this brief paper was attempted to summarize the current state of investigation in the field of bronchoalveolar lavage proteins.

Serum Identical Proteins

As reported by several investigators serum identical proteins are found in the bronchoalveolar lavage of the human [13, 14, 72, 73] and laboratory animals [56, 71]. In an extensive study Bell and co-workers [6] showed for the human 23 serum identical antigens (Table 1). As shown in own experiments [64] and also by others most serum proteins occure in the same distribution as measured in the blood serum [6, 28, 70, 83, 85]. The molecular weight of the serum identical proteins found in the bronchoalveolar lavage range up to 160,000 daltons indicating that there is a restriction in passage of high molecular weight proteins [5, 6]. The striking observation that IgG and IgA do occure in a higher level in bronchoalveolar lavage than in the serum is a result of the secretion of IgA, and perhaps also IgG, by lung tissue as components of the secretory immunological system of the mucosa [84]. These immunoglobulins were synthesized by lung tissue [32] and could be identified histologically in the mucosa and the extra-cellular lining of the lung [14, 15]. If there is additionally a selective transport of proteins across the mucosa-membrane similar to that across the placenta [84, 86] is not known.

In clinical trials it was attempted to determine the amount of particular proteins in correlation to total protein amount with the aim to use that correlation as diagnostic parameters. However, the concentration of serum-identical proteins in bronchoalveolar lavage could be influenced by artefacts. The occasional detection of alpha-2-macroglobulin in the bronchoalveolar lavage might be

Table 1. Serum identical proteins in lavage effluents from the lungs of healthy humans[a]

Protein	% of Total (mean ± SEM)[b]
IgG	19.0 ±1.7
IgA	10.2 ±1.0
IgM	0.08±0.04
IgD	0 ±0
IgE	0 ±0
β_1-Lipoprotein	0 ±0
α_2-Macroglobulin	0.34±0.18
Fibrinogen	0 ±0
C_4	0.38±0.03
C_3	0.98±0.09
Ceruloplasmin	0.30±0.03
Plasminogen	0 ±0
C-reactive protein	0 ±0
Haptoglobin	0.96±0.20
Transferrin	5.6 ±0.3
Hemopexin	0.85±0.09
Albumin	52.5 ±2.5
Prealbumin	0.09±0.01
α_1-Antitrypsin	3.5 ±0.3
Gc-globulin	0.24±0.02
α_2-HS-glycoprotein	0.65±0.06
α_1-Acid glycoprotein	0.74±0.12
β_2-Glycoprotein 1	0.16±0.02
Total	96.0

[a] according to Bell et al. [6] from George and Hook [25]
[b] $n=23$

the result of macrophage-activity, because these cells synthesize and secrete this protein [87]. Moreover, it could not be excluded that also other cells originally not derived from the lung, could secrete serum identical proteins.

An other striking report was given by Reifenrath and Zimmermann [71], who compared the albumin content of normal proceeded bronchoalveolar lavage fluid with such, obtained by micropuncture of the alveoli; because only small amounts of the serum albumin were found in the micropunctate they concluded that the content of serum proteins will be the result of blood contamination during the lavage procedure. Therefore until now the estimation of the concentration of serum-identical proteins in lavage has to be questioned and further studies must show how to quantify the proteins in lavage material before using them as a mirror of alveolar alterations. Methods with dilution techniques are not yet satisfactory [3].

Functional and Clinical Aspects of Serum Identical Proteins

The role of serum identical proteins in the alveolar lavage is still under discussion. There are only few

experimental datas until now. IgG and IgA probably protect the lung from virus and bacterial infection and also for transferrin an anti-bacterial effect was claimed [37, 47, 66, 69]. The alpha-1-antiproteinase is thought to prevent lung damage due to protease release from inflammatory cells [24]. This function is very important in lung diseases like emphysema or ARDS [23]. However, the relationship of these serum-identical proteins to the extra-cellular lining material concerning the surface tension lowering function till the current state of investigation is unknown.

Lung Specific Lavage Proteins

The question of whether specific extra-cellular lining proteins exist has induced a lot of work and in the meantime several reports were given, describing specific lavage proteins [8, 18, 21, 38–40, 44, 46, 48–52, 59, 62, 80, 81, 88]. The studies were mostly done on a variety of laboratory animals and only few reports were given for the human specific lavage proteins in the epithelial lining material [9, 10, 12, 77, 78]. The same was true for the human amniotic fluid representing a permanent bronchoalveolar lavage in the embryo [11, 41, 48].

One problem in the field of specific proteins of the extracellular lining material is however, that there are several different methods for the preparation of these proteins. It is obvious that different preparations leed to different results [64], and therefore it is difficult to describe all specific proteins for every laboratory animal.

Generally in the literature the specific lavage proteins were claimed as "apoproteins" because they do occure in preparations that have a surface lowering activity on a surface balance in-vitro [44]. In only few cases it was demonstrated, that the proteins possess a phospholipid-binding ability [53, 89]. Particularly for the human such an ability was never clearly demonstrated.

Despite the various different methods for the preparation some comparable lung specific lavage antigens were demonstrated for the human and laboratory animals. Out of them two proteins with molecular-weights, under reducing conditions, of about 36,000 daltons and 12,000 daltons have reached a generall interest. If lung specific proteins with a higher molecular weight were subjected to reducing conditions in nearly all experiments the 36,000 and 12,000 daltons subunits were found (Table 2). These observations perhaps indicate a similar function of these two proteins in the different species. There is no immunological cross-reac-

tion between the anti-sera and the 36,000 and 12,000 daltons proteins in different laboratory animals, except between human and monkey [78]. As Table 2 shows most of the studies were performed on these proteins while for proteins with a higher molecular-weight only a few reports exist.

Functional and Clinical Aspects of the Specific Lavage Proteins

Studies on bronchoalveolar lavage from patients with alveolar proteinosis indicated that the 36,000 daltons protein is present in a higher level in these patients than in the bronchoalveolar lavage from healthy non-smoking volunteers. This protein has been also detected in the amniotic fluid and increases in concentration in the amniotic fluid with advancing gestational age [77]. Establishing an enzyme-immuno-assay the 36,000 daltons protein in amniotic fluid has been used to determine the maturity of the fetal lung. The results are well correlated to the common lecithin-sphingomyeline ratio and the appearance of phosphatidylglycerol. Particularly in diabetic pregnancy the estimation of this specific protein is a better predictor for fetal lung maturity than the common used parameters [41]. – In experiments in rats with alloxan diabetes mellitus the 12,000 daltons protein was shown to decrease in comparison with the normal control [81]. It was speculated that this protein is a glycoprotein which is insufficiently synthesized in diabetes mellitus lung as it is known for carbohydrate and the phospholipids. One may speculate that also in other lung diseases the estimation of specific proteins of the extra-cellular lining material may be helpful as additional diagnostic parameter.

Our knowledge about the precise function of these proteins unfortunately is rather incomplete. Most of the proteins were identified as being associated with phospholipids [53, 89], and considered therefore to be important for a rapid film generation at the air-liquid-interface in the alveoli by providing a lipid protein arrangement together with calcium ions and including phosphatidylcholine and phosphatidylglycerol [82]. However, the nature of these protein-ion-lipid interaction is unknown but it is suggested that these aggregations may reduce the activation-energy for absorption and/or spreading of the phospholipids at the air-liquid-interface [7].

Doubtless our understanding of the function of the specific proteins of the extra-cellular lining in the alveoli and the terminal bronchi is limited. Concerning the important role of lowering the surface tension in the alveoli for preventing alveolar

Table 2. Lung specific proteins from different sources of the human and laboratory animals

Species	Origin	Molec. weight native	Molec. weight reduced		Additional characteristics	Involvement/Function	Reference No.
Human	Lavage	80,000	62,000	tryptic	amino acids known	in alveolar proteinosis	[12]
			36,000				
			26,000	degradation			
			16,000				
	Lavage	250,000			PAS pos.	enhanced in alveolar proteinosis	[76]
		62,000					
		36,000					
	Lavage	62,000			PAS pos.	in alveolar proteinosis	[67]
		36,000			PAS pos.		
	lung tissue homogenate	400,000	34,000		PAS pos.		[77]
		20,000					
	amniotic fluid	62,000			PAS pos.		[11]
		36,000			PAS pos.		
Rat	Lavage	160,000	38,000				[39, 40]
		140,000	32,000				
		110,000					
		78,000					
	Lavage	72,000	38,000			in Typ II cells	[88]
			34,000				
	Lavage	16,000				in diabetes mellitus content decreased	[81]
	Typ II cells		35,000		PAS pos.	DPPC-binding	[52, 80]
			10,000		PAS pos.	DPPC-binding	
Dog	Lavage	78–80,000	35–40,000		PAS pos.	DPPC-binding	[21, 51]
			10–12,000		PAS pos.		
	Lavage		35,000				
			10,000				
	Lavage	36,000				Lipid binding	[49]
	Lavage	70–80,000	35–45,000			DPPC-binding	[51, 52]
			10–12,000				
		72–73,000	36,000				
Rabbit	Lavage	340,000			PAS pos.		[59]
	Lavage		62,000		PAS pos.		[8]
	Lavellar bodies		36,000		PAS pos./IEP 7.4		
Sheep	Lavage		34,000				[46]
	Lavage		120,000				[21]
			35,000				
			30,000				
			10,000				
Chicken			62,000				[8]
			35,000				

collaps and fluid overload research in this particular field would be important for a better understanding of lung structure and function in health and disease. More work on biochemical background and physiological function is needed and we like to emphasize too, the need of clinical trials to establish the diagnostic value of the lung specific proteins in lung diseases. One may speculate that this may leed to diagnostic tools like those used to determine lung maturity in amniotic fluid.

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