Comment

Surfactant protein B and mimic peptides in the function of pulmonary surfactant

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Gustafsson et al. [1] have studied by circular dichroism and Fourier transform infrared spectroscopy the structure and orientation in a phospholipid environment of the 21 residue peptide KLLLLKLLLLKLLLLKLLLLK (KL_4), a mimic of surfactant protein B (SP-B) [2]. The lipid environment was provided by DPPC/PG 7:3 (w/w) in an aqueous dispersion. One goal of the study was to test the original hypothesis [2] that in a monolayer of DPPC and PG, namely at an air-water interface along the alveolar surface in the lung, the KL_4 peptide binds to the phospholipid molecules by virtue of hydrostatic interactions of the charged lysine residues with polar head groups, and by stretches of hydrophobic leucine residues of the KL_4 with phospholipid acyl side chains.

The authors conclude that the KL_4 peptide adopts a transmembranous orientation in the bilayer through spectroscopic evidence that indicates that the KL_4 peptide lies parallel to the acyl side chains. They add that 'this is in sharp contrast to the mechanism of action first proposed for SP-B and KL_4 [2]'. They note that the originally proposed interactions between KL_4 and the phospholipid molecules 'are difficult to envision with the KL_4 helical surface and orientation in a phospholipid bilayer now found, suggesting another mechanism of action for KL_4 in pulmonary phospholipids'.

A major difficulty in the interpretation of data by Gustafsson et al. is that they have compared the orientation of the KL_4 peptide in a *bilayer* with the orientation of the peptide in a *monolayer* as originally proposed [2]. As they point out, in a bilayer, only the centrally situated lysine (Lys-11) would lie in the total non-polar, hydrocarbon environment, while the amino groups of the remaining lysines (Lys-1, 6, 16 and 21) would interact with the phospholipid head groups. Such electrostatic interactions are exactly what was originally proposed for KL_4 peptide and SP-B in the environment of phospholipid molecules in a *monolayer* of pulmonary surfactant [2], with the exception that Lys-11 along with all the lysine residues, would also interact with the polar head groups. It is these strong electrostatic interactions along with the hydrophobic and van der Waals interactions between hydrophobic stretches of the protein and acyl side chains of the phospholipids that provide the lateral strength or ordering of phospholipid molecules in a monolayer by SP-B or its mimic peptides in pulmonary surfactant (Fig. 1) [3]. Such ordering is essential for long-term stability of the surfactant.

Gustafsson et al. also compare the activity of phospholipid dispersions of KL_4 peptide and SP-C over a 60 second period at 30°C in a Wilhelmy balance, finding the KL_4 peptide dispersions somewhat less active. It must be noted that more than two years were spent in the original studies [2] to determine the precise constituents, their sources of production and method of formulation into aqueous dispersions for the optimal production of KL_4-surfactant. It is thereby understandable that these authors may not have achieved optimal activity. In addition, KL_4-surfactant was originally formulated on the basis of SP-B, to produce long-term stability of the surfactant monolayer, and not necessarily to produce a response of 60 second duration at 30°C. Possibly on this basis, a single instillation of KL_4-surfactant generally served to provide permanent normal pulmonary function to preterm human infants in a Phase 2 clinical study [4] and for at least a 24 hour period in preterm rhesus monkeys [5]. It should be noted that Gustafsson et al. were probably unaware of these latter data since they were published after the study by Gustafsson et al. was in press.

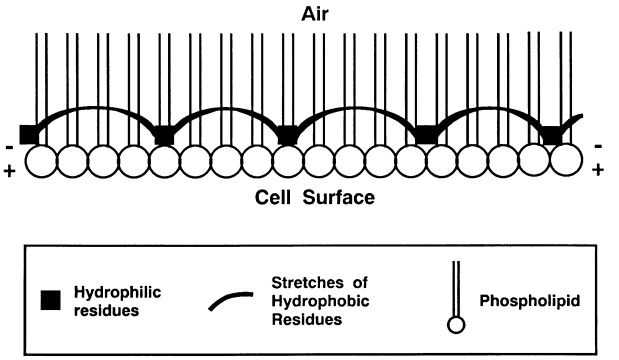

Fig. 1. Two-dimensional theoretical representation of the mechanism of function of SP-B protein and mimic peptides in the PL monolayer. The hydrophilic, charged residues interact with polar head groups of the PL, whereas the hydrophobic stretches of the peptide interact with the acyl side chains. These interacting forces induce stabilization of the PL layer, providing greater capacity to resist surface tension or alveolar collapse. (Reproduced with permission of Science.)

References

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