Surfactant protein SP-C and cholesterol modulate phase segregation in lung surfactant membranes

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Breathing is sustained by the presence of lung surfactant (LS), a surface active agent lining the alveolar air-liquid interface. This lipid-protein complex develops a complex meshwork of lipid assemblies that reduce surface tension, and so allows lungs to compress and expand normally with minimal energy requirements. Cholesterol is the major neutral lipid in surfactant, but its precise role is a matter of debate. In some instances, cholesterol presence can impair surfactant function, an effect that can be reversed by the presence of the lipopeptide SP-C, the smallest and most hydrophobic protein present in LS complexes. In this work, the combined effect of SP-C and cholesterol on LS-mimicking membranes has been assessed by deuterium Nuclear Magnetic Resonance (2H-NMR) and Electron Spin Resonance (ESR). Our results show that SP-C induced phase segregation at physiological temperatures leading to the generation of a highly ordered, possibly interdigitated, phase and a liquid crystalline phase. All the lipids forming part of the LS model system, DPPC, POPC and POPG, were affected by SP-C-induced phase segregation to different extents, revealing SP-C specificity for certain lipid environments. The combination of SP-C and cholesterol also resulted in an ordering effect, but evidence of phase segregation was only observed at 30^{o}C. The use of deuterated cholesterol did not show signs of any specific lipid-protein interactions, whereas SP-C palmitoylation appeared as an important factor maximizing the differences among lipids forming part of every phase. These results illustrate how the complex surfactant structure can be finely tuned by a balanced action of cholesterol and SP-C, which display combined effects regulating surfactant structure and dynamics.