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Cholesterol-binding Cyclodextins for the Treatment of Cystic Fibrosis and Other Diseases with Pulmonary Surfactant Dysfunction

Cystic Fibrosis (CF) is a life-threatening genetic disorder where thick mucus is built up in the lungs, causing severe respiratory problems and complications (such as bacterial infection and inflammation).

Pulmonary surfactant (PS) is a surface active substance lining the respiratory system of mammalian lung secreted by type-II alveolar epithelial cells [1]. It is a thin lipid-protein film at the air–liquid interface in the lungs. Its function is to dynamically control the surface tension of the boundary surface during the breathing cycle. The surface tension of water is about 70 mN/m, but in the lungs only about 25 mN/m, which is further decreased to near 0 mN/m when the PS film becomes compressed at the end of expiration. This low surface tension controlled by PS decreases the pressure difference between inflation and deflation of lung and as a consequence reduces the work of breathing and prevent alveolar collapse at low lung volumes. The surface forces help also to get rid of the inhaled particles. PS dysfunction results in impaired ability of lung to expand, in decreased lung volume, reduced airway patency and hypoxia.

PS contains ~90% lipid and ~10% surfactant-specific protein. In addition to the main lipid component, the zwitterionic and highly surface active dipalmitoyl phosphatidyl choline (DPPC) (40–45%) [2], further disaturated and some unsaturated phosphatidyl cholines (~35–40%), negatively charged phosphatidyl glycerol (5–10%) and 5–8% neutral lipid (mainly cholesterol) build up the layer (Fig. 1) [3,4]. The proteins modulate the surface active properties of the surfactant lipids, give mechanical strength to the monolayer, help the monolayer-bilayer transition during expansion and contraction phases and play important role in innate defense mechanisms of the lung [5,6].

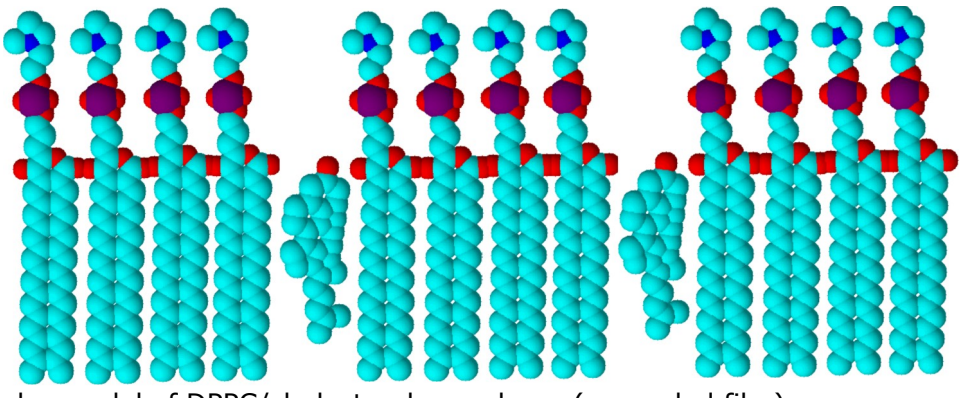

Fig. 1 Molecular model of DPPC/cholesterol monolayer (expanded film)

Role of Cholesterol

The role of cholesterol is maintaining PS in a relatively fluid state, ensuring its lateral organization and providing mechanical plasticity [7]. The cholesterol/phospholipid ratio changes rapidly within a narrow range on physiological stimuli. For instance, the cholesterol content changes with exercise to accommodate PS to the need of enhanced ventilation [4]. However, extremely enhanced cholesterol levels were found in PS dysfunction, such as in acute lung injury (ALI), acute respiratory distress syndrome (ARDS), ventilation-induced lung injuries (VILI) and also in cystic fibrosis (CF) [8–10].

If PS contains elevated proportion of cholesterol (>20%) phase separation of the hydrophobic fraction of PS occurs. On the other hand, decreasing the cholesterol level by extracting cholesterol using methyl BCD causes dramatic changes in the lateral structure and spreading properties at the air-liquid interface [7]. A finely tuned lipid composition (different among species and among individuals) seems to be a prerequisite of the normal function.

Similarly to other biomembranes PS is also characterized by the coexistence of liquid-ordered (L_o) and liquid-disordered (L_d) phases (raft hypothesis) in dynamically changing arrangement. The rafts (more condensed phases surrounded by less condensed phase) can be visualized by atomic force microscopy [11]. In the presence of elevated cholesterol level the number of liquid-ordered microdomains increased while their size decreased from about 10 μm to 3–6 μm. Removal of cholesterol by methyl BCD resulted in restored phase behavior: the number and size of the microdomains became similar to the PS without cholesterol (5–10 μm) (Fig. 2). The studies with deuterated cholesterol proved that cholesterol is located mostly within the L_o phases.

The presence of the domains, the coexistence of liquid-expanded and liquid-condensed phases as well as the liquid-ordered (L_o) and liquid-disordered (L_d) phases makes possible the regulation of surface tension [12].

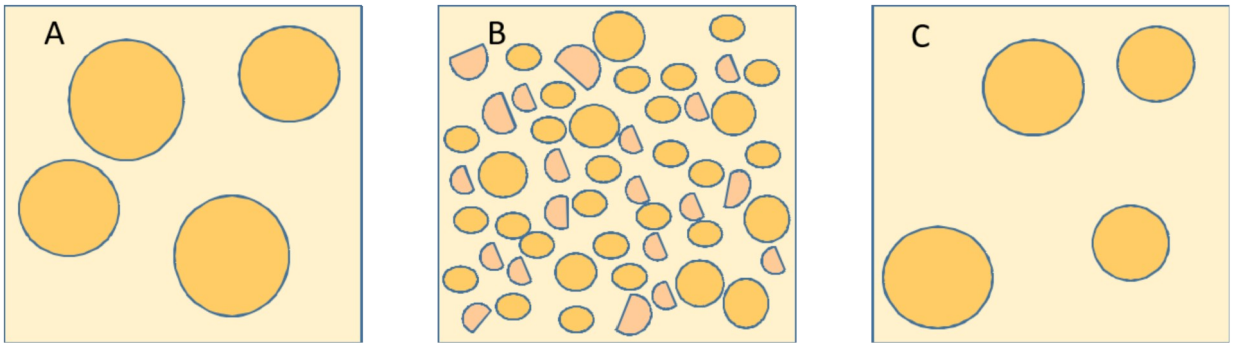

Fig. 2 Scheme of the liquid-ordered microdomains in the contracted PS films untreated (A), with added cholesterol (20 mol%) (B), and after removal of cholesterol with methyl BCD (C).

Effect of methyl BCD

Bovine lipid extract surfactant (BLES) used in the surfactant replacement therapies in neonatal respiratory distress syndrome contains almost all the components of human PS but only 1.5 mol% cholesterol [8]. Diseased lung was mimicked by addition of 20 mol% and 30 mol% cholesterol (related to phospholipids) either dissolved in organic solvent or in the form of water-soluble cholesterol (solubilized by methyl BCD). These cholesterol-enriched BLES films were not able to reduce the surface tension below 16 mN/m upon compression. Treating them with 40 mg/mL methyl BCD restored the surfactant function (near zero mean surface tension). The function of BLES itself (not loaded with cholesterol) was not influenced by the presence of methyl BCD [8].

In another experiment BLES was supplemented with free fatty acids and lysophosphatidylcholine as typical compounds formed after oxidative stress in PS [13]. These

compounds inhibit PS function in dose-dependent manner, but in a lower extent than cholesterol. The inhibition was reversed by methyl BCD even in relative absence of cholesterol suggesting that methyl BCD can sequester also non-steroidal lipids.

In vivo experiments with PS-deficient rats (PS was removed by lavage of lungs with saline) showed the importance of PS in arterial blood oxygenation levels [11]. The oxygenation level remained low for the PS-deficient animals not receiving any treatment, while those treated with BLES showed significantly improved oxygenation which was worse when BLES was added together with 20 mol% cholesterol (Fig. 3).

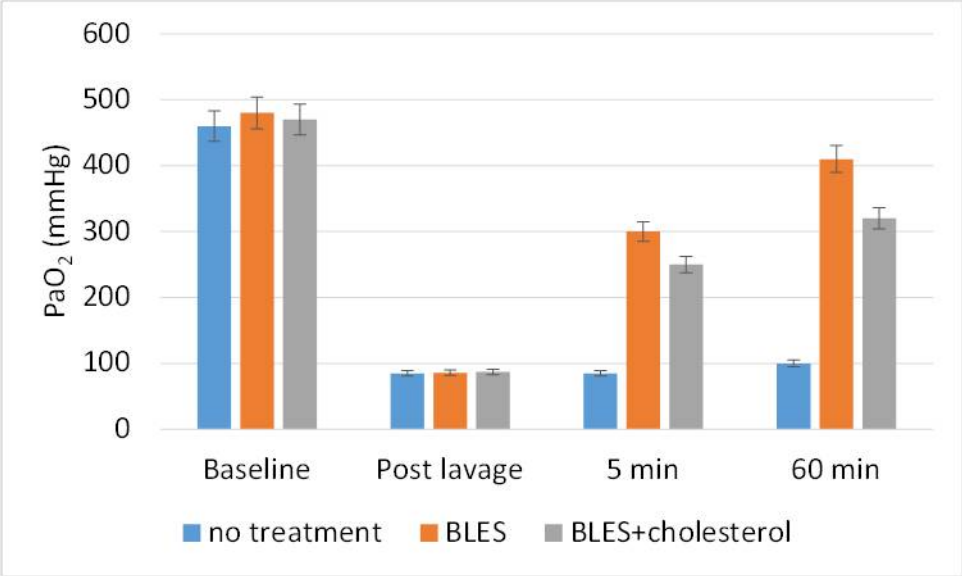

Fig. 3 Mean arterial blood oxygenation (PaO_2) of PS-deficient rats treated with 20 mg/kg phospholipid (BLES) and with 20 mg/kg phospholipid (BLES) + 20 mol% cholesterol (drawn from the data in ref. 11)

In another experiment, rats were mechanically ventilated to induce VILI [14]. The rats in group of high-tidal volume (HTV) ventilation showed lower oxygenation values after 90 min of ventilation than the rats in the low-tidal volume group (LTV). The surfactant samples obtained by lavage of lungs showed significant difference: PS of HTV group demonstrated much lower surface activity compared to LTV group. Removal of cholesterol by methyl BCD from the PS samples of HTV group improved the ability to reduce the surface tension, while the replacement of cholesterol again impaired the surface activity.

Recent *ex-vivo* studies using human samples from pediatric patients in cystic fibrosis (26 CF patients aged of 1–12 years) and from patients without this disease (9 patients aged of 1–15 years) (lung-healthy control) showed that the basic abnormality was the elevated cholesterol concentration in the bronchial lavage fluid and the interaction between cholesterol and oxidized phospholipids [13]. In cystic fibrosis the small airways are the region of the lung most severely affected by inflammation and infection. The surface activity of PS obtained from the small airways was markedly impaired compared to control samples: the minimum surface tension was >12 mN/m for CF samples. The cholesterol content was much higher in CF patients (13%) compared to lung-healthy control (5%). Methyl BCD significantly improved the surfactant action (near zero surface tension) in a majority of the samples.

Concluding remarks

The high affinity of methyl BCD toward cholesterol not only gives a tool to the researchers for studying the effect of cholesterol on the function of PS, but also seems to offer a new therapeutic strategy for the treatment of pathologies with PS dysfunction. A patent application describing the method has been filed: By removing cholesterol from pulmonary surfactant

through the addition of a cholesterol-sequestering agent, oxidative damage to the surfactant is mitigated. It was also shown that normal function can be restored by methyl-beta-cyclodextrin to dysfunctional surfactant removed from the lungs of children with cystic fibrosis and noncystic fibrosis bronchiolitis [15].
Although in the Scopus there are 260 papers on CDs beneficial effects on pulmonary delivery of various drugs, we at CycloLab are not aware of any marketed, CD-enabled formulations for pulmonary administration. One of the possible explanations that CDs themselves are absorbed through the respiratory mucosa: when BCD, DIMEB and HPBCD were administered by intratracheal instillation to rabbits, the bioavailability of CDs was 66%, 74% and 80%, respectively [16]. In vivo, it was demonstrated that short-term exposure to inhaled HPBCD, GCD and RAMEB solutions are non-toxic after assessing bronchoalveolar lavage, lung and kidney histology, bronchial responsiveness to methacholine and blood urea [17].

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Éva Fenyvesi

CycloLab Cyclodextrin R&D Laboratory, Ltd.,

Budapest, HUNGARY

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Functioning via host-guest interactions

Review, Self-healing properties under semi-dry conditions, Crosslinking density, Distances between the crosslinking points, Actuators, Contractive bending behavior

Journal of Inclusion Phenomena and Macrocyclic Chemistry, 2017, 87, 313-330; DOI:10.1007/s10847-017-0702-z

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Efficient extracellular recombinant production and purification of a Bacillus cyclodextrin glucanotransferase in Escherichia coli

Novel purification method for the CGTase using starch adsorption

Microbial cell factories, 2017, 16, 87; DOI: 10.1186/s12934-017-0701-1

Schmidt, B.; Barner-Kowollik, C.

Dynamic Macromolecular Material Design - The Versatility of Cyclodextrin Based Host/Guest Chemistry

Review, Macromolecular building blocks, Extraordinary adaptive property

Angewandte Chemie (International ed. in English), 2017, 56, 8350-8369; DOI: 10.1002/anie.201612150

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Determinants of the host-guest interactions between α-, β- and γ-cyclodextrins and group IA, IIA and IIIA metal cations: a DFT/PCM study

Metal affinity/selectivity, α-, β- and γ-CDs. Density functional theory (DFT) polarizable continuum model (PCM)

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Thatiparti, T. R.; Juric, D.; von Recum, H. A.

Pseudopolyrotaxane Formation in the Synthesis of Cyclodextrin Polymers: Effects on Drug Delivery, Mechanics, and Cell Compatibility

Three diglycidylether cross-linkers, Affinity-based drug delivery

Bioconjugate Chemistry, 2017, 28, 1048-1058; DOI:10.1021/acs.bioconjchem.6b00721

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Ring Shuttling Controls Macroscopic Motion in a Three-Dimensional Printed Polyrotaxane Monolith

Amplification of molecular motions into the macroscopic world, Direct-write 3D printing, α-CDs, Poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) (PEO-PPO-PEO) triblock copolymers, Macroscopic shape-memory properties, Converting the chemical energy input into mechanical work, Lifting objects against gravity

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Pulmonary surfactant dysfunction in pediatric cystic fibrosis: Mechanisms and reversal with a lipid-sequestering drug

Excess of cholesterol, Lipid-sequestering agent, Methyl-β-CD, Restored surfactant function

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Kameyama, K.; Motoyama, K.; Tanaka, N.; Yamashita, Y.; Higashi, T.; Arima, H.

Induction of mitophagy-mediated antitumor activity with folate-appended methyl-β-cyclodextrin

Endocytosis, Transmembrane potential of isolated mitochondria, Adenosine triphosphate (ATP) production, Active oxygen species production, Autophagic cell death

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Intrathecal route, IV infusions, Intracerebroventricular route, Adverse events, Loss of hearing, Chemical meningitis

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Methyl-β-cyclodextrin, 2-HPBCD, Lipids depleted from LDL, Inhibitory effect on lipoxygenase-induced LDL oxidation, Inhibition of atherogenesis

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Self-Assembly of Amphiphilic Biotransesterified β-Cyclodextrins: Supramolecular Structure of Nanoparticles and Surface Properties

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Cutaneous wound healing, Traditional herbal medicine, HPBCD-tetracapped hyperforin, ATP release

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Evaluation of porphyrin loaded dry alginate foams containing poloxamer 407 and β-cyclodextrin-derivatives intended for wound treatment

Dry alginate foams, Antibacterial photodynamic therapy of infected wounds, MethylβCD (MβCD), DIMEB, HPBCD, Fast disintegration

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Inhibitor of DNA topoisomerase-I, Inhibited tumor cell adhesion to vascular endothelial cells, Mice

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γ-CD coordinated to alkali metal cations, Bioavailability, Rapid uptake, Longer half-life

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Polymeric βCyD nanoparticles, Confined microdomains inside the crosslinked nanoparticles, Double modality of complexation

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Docetaxel-Loaded Nanoparticles Assembled from β-Cyclodextrin/Calixarene Giant Surfactants: Physicochemical Properties and Cytotoxic Effect in Prostate Cancer and Glioblastoma Cells

Self-assembly, Core-shell nanospheres or nanocapsules, High docetaxel loading capacity, Initial fast release of the drug followed by a slow and sustained release rate, Glioblastoma, Prostate cancer

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Detection and Removal of Endogenous Carbon Monoxide by Selective and Cell-permeable Hemoprotein-model Complexes

Covalently attached an octaarginine peptide to a maleimide-appended hemoCD1, Expedient for exploring specific and still unidentified biological functions of CO in cells

Potential therapeutic application of dendrimer/cyclodextrin conjugates with targeting ligands as advanced carriers for gene and oligonucleotide drugs

Polyamidoamine dendrimer (G3) conjugates with α-CyD, Cell-specific drug carriers, Polyethylene glycol, galactose, lactose, mannose, fucose and folic acid-appended α-CDEs

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Cyclodextrin-mesoporous silica particle composites for controlled antibiotic release. A proof of concept toward colon targeting

"Gatekeeper" agents, Metronidazole, Clofazimine, Triggered release formulation, Targeting bacterial infections in the colon and lower intestine

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Dietary α-cyclodextrin reduces atherosclerosis and modifies gut flora in apolipoprotein E-deficient mice

apoE-knockout mice, Low-fat diet, Western high fat diet containing either no additives (WD), 1.5% α-CD (WDA); 1.5% β-CD (WDB); or 1.5% oligofructose-enriched inulin (WDI), Decreased plasma cholesterol levels, Decreased aortic atherosclerotic lesions, Decreased cecal bacterial counts in genera Clostridium and Turicibacterium, Increased Dehalobacteriaceae

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Influence of the Form of Administration of Chlorogenic Acids on Oxidative Stress Induced by High fat Diet in Rats

Green coffee, Chlorogenic acids added to bread, Reduced absorption from the crumb in the small intestine and increased passage to the colon, Beneficial modification of enzymic activities of intestinal microbiota, Increased bioaccessibility

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Removal of 17β-estradiol from aqueous solutions, Langmuir models, Regeneration

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Highly Efficient, Green, and Scalable β-Cyclodextrin-Assisted Aqueous Exfoliation of Transition-Metal Dichalcogenides: MoS2 and ReS2 Nanoflakes

Transition-metal dichalcogenide nanosheets, Hydrogen evolution reactions, Noble-metal-free catalysts

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Edited and produced by: CYCLOLAB
Homepage: www.cyclolab.hu
H-1525 P.O. 435, Budapest,
Hungary
Tel.: (+361)347-6060
Fax.: (+361)347-6068
e-mail: cyclolab@cyclolab.hu