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Cyclodextrin-assisted reconstitution of membrane proteins

Membrane proteins are important drug targets. Functional and structural studies of these proteins is of growing importance but more difficult than studies with soluble proteins because membrane proteins function in lipid bilayers of cell membranes. Their study under *in vitro* conditions requires membrane-mimetic environment. Especially the channels and transporter proteins should be reconstituted into lipid bilayers. This is particularly obvious for membrane transporters, because they – unlike for instance membrane receptors or enzymes – are only able to perform their transport function in the membrane-embedded form. After detergent-mediated solubilization and purification of proteins, detergents have to be removed from the reconstitution mixture to achieve the proper incorporation of the proteins into lipid bilayers, e.g. into liposomes. The reconstitution process, in which detergent is replaced by lipid, must be carefully controlled to avoid denaturation and aggregation of the proteins.

There are various methods used for detergent removal (dilution, chromatography, dialysis, and adsorption). These methods, however, are not selective enough and may result in heterogeneous vesicles. Dilution results in low protein concentration which makes the further experiments difficult. Dialysis is time-consuming (may last for weeks) with the risk of denaturation of the protein. Adsorption of the surfactant on polystyrene beads is too fast and uncontrolled often resulting in aggregation of the protein.

The selective detergent extraction from detergent/lipid/protein micelles by cyclodextrins was first described by Degrip et al. (1998). The approach is based on the much higher affinity of CD for detergents in comparison with bilayer-forming lipids. The detergent/CD complexes can be easily removed by centrifugation through a discontinuous sucrose gradient (Fig. 1). A variety of detergents was tested in this procedure on the bovine rod visual pigment rhodopsin in combination with retina lipids. In all cases good yields of proteoliposomes were obtained, which contained fully functional rhodopsin.

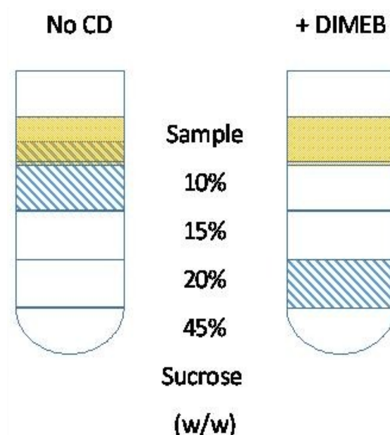

Fig. 1. Separation of surfactant (yellow layer) from proteoliposomes (blue striped layer) in the absence and presence of DIMEB. The sample containing of rhodopsin dissolved in 20 mM n-dodecyl-β-D-maltoside (DDM) as surfactant and lipid mixture was layered on the top of the sucrose layers. After centrifugation the proteoliposomes migrated into the 20% or 45% sucrose layer in the absence and presence of 10 mM DIMEB, while the surfactant/CD complex remained on top of the gradient. (Redrawn after Degrip et al. 1998)

The GRecon method applies CD and lipid gradient combined with sucrose gradient. As the protein migrates into the gradient during ultracentrifugation the detergent is gradually included by CD and the protein is incorporated into the preformed liposomes (Fig. 2) (Althof et al. 2012). Detergent removal starts slowly and then progresses as the protein migrates into the gradient. This method separates effectively proteoliposomes from empty liposomes. The method was successfully applied for reconstitution of both large and small proteins, such as mitochondrial supercomplexes, BN-PAGE, and the 56 kDa carnitine transporter CaiT from *E. coli*.

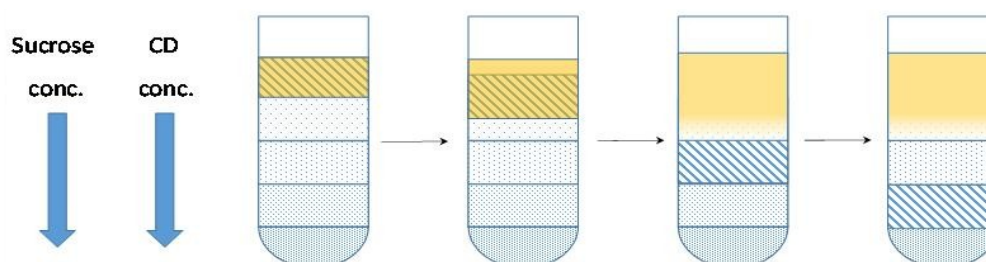

Fig. 2. Separation of surfactant (yellow layer) from proteoliposomes (blue striped layer) using gradients of CD. During centrifugation the detergent is gradually replaced by the lipid.

CD is claimed to have a higher affinity for detergents than for lipids, thus preventing changes in the lipid to protein ratio during reconstitution. CD is selected based on affinity to the detergent: α-CD is suitable for surfactants with long alkyl chain, such as n-dodecyl-β-D-

maltoside (DDM) or *n*-dodecyl-β-D-thiomaltopyranoside (DOTM) (Fig. 3) and γ-CD is used for sequestration of bile-salt-derived detergents, such as digitonin (Fig. 4). Methyl β-cyclodextrin was used for removal of detergent from ternary mixtures of protein, detergent and lipids to get 2D crystals of OmpF, a typical β-barrel protein, and with SoPIP2;1, a typical α-helical protein (Signorelli et al. 2007) as well as to remove DDM or DOTM for studying bacteriorhodopsin (BR), a photoactivable proton pump that produces a transmembrane-stable and light-switchable electrochemical gradient of protons (Dezi et al. 2013). β-cyclodextrin (most probably methyl BCD) was used for the reconstitution of Na^+/galactose cotransporter (vSGLT) of *Vibrio parahaemolyticuseta* (Turk et al. 2000). In the latter case the liposomes consisted of soy lecithin and cholesterol and it was not studied weather the structure of the lipid bilayer changed upon the complexation of cholesterol and if cholesterol or decyl-β-D-maltoside (C10M) are the preferred guest molecules for inclusion into the β-CD cavity.

CD is used in stoichiometric ratio to detergent: the molar ratio of CD/detergent is preferably in the range of 1.2:1 to 2.4:1 (Althof et al. 2012).

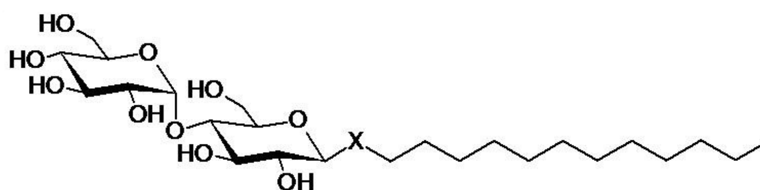

Fig. 3. Structure of n-dodecyl-β-D-maltoside (X = O) and n-dodecyl-β-D-thiomaltoside (X = S), widely used detergents for isolation and purification of proteins

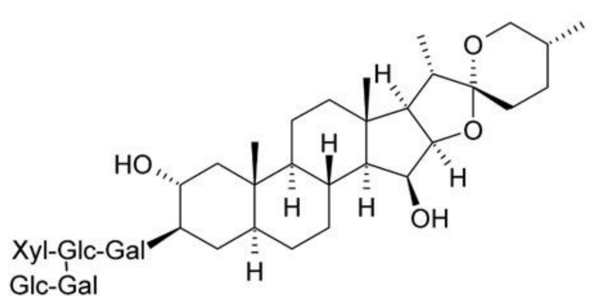

Fig. 4. Structure of digitonin, widely used detergent solubilizing membrane proteins, precipitating cholesterol and permeabilizing cell membranes (Pitha and Szente 1984)

Giant unilamellar vesicles (GUV) are increasingly used for studying biophysical and biochemical processes related to cell functions. Planar membranes (polymer-supported membranes, PSM) providing mobility for lipids and proteins were also developed. Unilamellar vesicles containing transmembrane proteins were generated by detergent depletion with CD and captured by ultrathin poly(ethyleneglycol) polymer brush functionalized with fatty acid moieties (Roder et

al. 2011). The fusion of vesicles on the surface of the polymer resulted in a planar membrane useful for studying transmembrane receptor proteins.

The method was fully automatized. The 2DX Robot prepares 2D crystals for studying membrane proteins by electron crystallography, atomic force microscopy and solid state NMR (Iacovache et al. 2010). The method requires smaller volumes and lower protein concentrations than established 2D crystallization methods, making it possible to explore more conditions with the same amount of protein. The method yielded highly ordered 2D crystals diffracting to high resolution from the pore-forming toxin *Aeromonas hydrophila* aerolysin (2.9A), the plant aquaporin SoPIP2;1 (3.1A) and the human aquaporin-8 (hAQP8; 3.3A).

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Poly(L-lysine), Bisphenol A, Imprinting, Allosteric effects

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Antibacterial activity, Wound healing activity, Polyethylene glycol, Sodium dodecyl sulfate, β-CD, Antibacterial activities, Gelling agents

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Cyclodextrin polymer, Glioblastoma, Metalloproteinase

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Ciprofloxacin, β-CD, Sustained release, Blood compatibility, Bone tissue engineering

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α-CD, Porcine skin, Modified gold substrates

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Cyclodextrin, Lipid-membrane-incorporated fullerene derivatives

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Anticancer activity, Click reaction, Sustained release

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Camptothecin, Inclusion complex with β-cyclodextrin, Semiamorphous or amorphous CPT

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Glycosphingolipids, Pentadecapeptide, Methyl-β-cyclodextrin

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Review, Cholesterol, Fatty acids, Phospholipids, Sphingolipids, Alpha-cyclodextrin, Beta-cyclodextrin, Methylated beta-cyclodextrin, Membranes

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Nonviral vectors, β-Cyclodextrin/ferrocene host-guest recognition

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β-Cyclodextrin-grafted TEMPO-oxidized cellulose nanofibers for sustained release of essential oil

Carvacrol, Packaging system for food

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Hydroxyethyl-β-cyclodextrin, Initial extraction rate

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Inclusion complex, Molecular dynamics simulation, 1-Bromooctane, β-CD

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Wastewater, Phosphonobutanetricarboxylic acid

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β-CD, Micro-pores, Permeability selectivity

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Microfiltration, Visible-light driven photocatalytic degrdation

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Supercritical drying of organogels, Isocyanates, Mechanical properties, Nano-cavities, Micropores, Mesopores

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Homoallyl sulfide, Catalytic system, Assistance of cyclodextrin

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Glucose, Reducing agent, Disposable sensor

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Nanocrystals, Biomimetic catalysts, Peroxidase-like activity, β-Cyclodextrin

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Methyl-β-cyclodextrin, Chiral selector, Naproxen, Warfarin, Pranoprofen

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Review, Size control, Therapeutic agent/imaging component

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Azobenzene, β-CD-mannose conjugates, Measurement of bacteria

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Food quality control, Glassy carbon electrode

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