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Phospholipid demixing and the birth of a lipid droplet

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ABSTRACT

The biogenesis of lipid droplets (LD) in the yeast *Saccharomyces cerevisiae* was theoretically investigated on basis of a biophysical model. In accordance with the prevailing model of LD formation, we assumed that neutral lipids oil-out between the membrane leaflets of the endoplasmic reticulum (ER), resulting in LD that bud-off when a critical size is reached.

Mathematically, LD were modeled as spherical protuberances in an otherwise planar ER membrane. We estimated the local phospholipid composition, and calculated the change in elastic free energy of the membrane caused by nascent LD. Based on this model calculation, we found a gradual demixing of lipids in the membrane leaflet that goes along with an increase in surface curvature at the site of LD formation. During demixing, the phospholipid monolayer was able to gain energy during LD growth, which suggested that the formation of curved interfaces was supported by or even driven by lipid demixing. In addition, we show that demixing is thermodynamically necessary as LD cannot bud-off otherwise.

In the case of *Saccharomyces cerevisiae* our model predicts a LD bud-off diameter of about 12 nm. This diameter is far below the experimentally determined size of typical yeast LD. Thus, we concluded that if the standard model of LD formation is valid, LD biogenesis is a two step process. Small LD are produced from the ER, which subsequently ripe within the cytosol through a series of fusions.

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1. Introduction

Lipid droplets (LD) are depots for neutral lipids (NL). They exist in virtually all kind of living cells, from bacteria, to yeasts, to plants and mammals. A LD consists of a hydrophobic, NL-containing core surrounded by a phospholipid (PL) monolayer containing a small amount of proteins (Martin and Parton, 2006). In *Saccharomyces cerevisiae*, LD are mainly formed by triacylglycerols (TAG) and steryl esters (SE) in roughly equal amounts (Leber et al., 1994; Czabany et al., 2007, 2008). Conversion of free fatty acids (FA) and sterols to NL and their subsequent storage in LD is an organism's strategy to risklessly save intrinsically toxic FA and sterols for later use. If required, FA and sterols may be rapidly released from LD and used as pre-fabricated building blocks for membrane lipid synthesis as well as other complex lipids, and/or as source of chemical energy (Murphy and Vance, 1999; Fujimoto et al., 2008; Zanghellini et al., 2008). Also, LD are assumed to have a function in transporting sterols to the plasma membrane (Czabany et al., 2007). Indeed, it is now recognized that rather than being inert storage pools, LD are remarkably flexible, dynamic organelles (Fujimoto et al., 2008; Murphy et al., 2009; Olofsson et al., 2009).

LD biogenesis is everything but clear. According to a widely accepted model, NL accumulate within distinct regions of the endoplasmic reticulum (ER) membrane, initially forming a lens-shaped and then a spherical bulge in the membrane (Fig. 1). After reaching a critical size, mature LD will bud-off, being encapsulated in a PL monolayer that is directly derived from the cytoplasmic ER leaflet (Murphy and Vance, 1999; Murphy, 2001; Martin and Parton, 2006; Czabany et al., 2007; Fujimoto et al., 2008). This budding model is in line with several experimental findings: (i) In yeast the same ER proteins, except for very few, are also detected on the LD membrane (Huh et al., 2003; Natter et al., 2005). (ii) Most LD proteins lack transmembrane spanning domains (Athenstaedt et al., 1999). (iii) In yeast mutants, which are unable to synthesize TAG and SE, LD do not form. Nonetheless all typical LD proteins are found in these strains, but now solely localized to the ER (Sorger et al., 2004) and the cytosol. It has also been hypothesized that developing LD might not bud-off, but are cut out from the ER in form of bicelles, leaving a transient hole in the ER membrane (Ploegh, 2007).

Abbreviation: ER, Endoplasmic reticulum; FA, Fatty acid; LD, Lipid droplet; LPC, Lysophosphatidylcholine; NL, Neutral lipid; O-LPC, oleoylphosphatidylcholine; PA, Phosphatidic acid; PC, Phosphatidylcholine; PE, Phosphatidylethanolamine; PI, Phosphatidylinositol; PL, Phospholipid; PS, Phosphatidylserine; SE, Steryl ester; TAG, Triacylglycerol.

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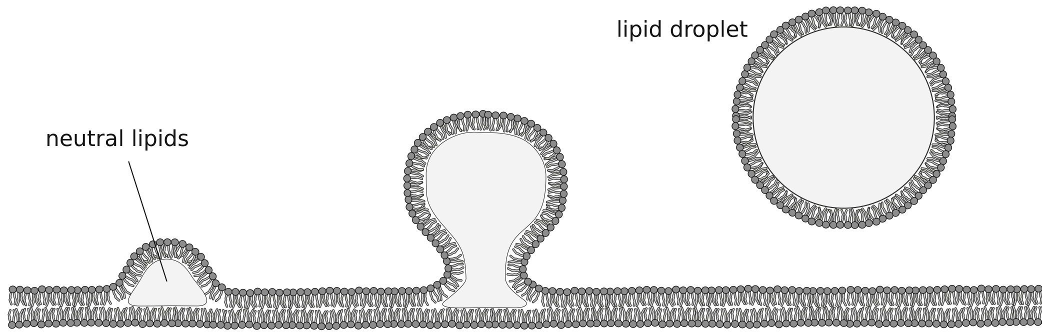

Fig. 1. LD formation according to the standard model. During their biosynthesis NL "oil-out" in between the leaflets of the ER bilayer, forming spherical structures. Mature LD then bud-off and form independent organelles.

A nascent LD trapped within the leaflets of the ER has never been observed experimentally, thus other mechanisms for its formation have been suggested. See Walther and Farese (2009), Thiele and Spandl (2008) for reviews. The most prominent alternative is based on vesicular budding (McMahon and Mills, 2004; Praefcke and McMahon, 2004; Corda et al., 2006). In such a process small bilayer vesicles are formed, which are subsequently filled with NL (Robenek et al., 2005, 2006). As yet, neither model has been conclusively verified experimentally. Whether this has to be attributed to low resolution of microscopic approaches or indicates that the proposed scenarios are wrong is still a matter of debate. In this article we take up the former position. Moreover, we here assume that LD formation takes place according to Fig. 1. That is to say, NL-filled bulges are formed in the cytosolic monolayer of the ER membrane, from where they subsequently bud-off. Taking this scenario seriously, we calculate biophysical consequences for the process of LD biogenesis.

Our analysis has been motivated by experimental findings in yeast that the PL monolayer composition of LD differs from the one of the ER membrane (Zinser et al., 1991; Leber et al., 1994; Tauchi-Sato et al., 2002). This suggests that the PL composition is related to the local curvature of the monolayer in agreement with similar observation from theory and experiment (Roux et al., 2005; Jiang and Powers, 2008). Lipids with a cone-like molecular shape (inducing a positive or convex curvature) are expected to be more adapted to the spherical surface of LD than wedge-like shaped ones, which induce a negative or concave curvature. Thus, the former should be enriched on LD surfaces (relative to their value in the ER membrane) while the latter ought to be depleted. For instance, due to their geometrical shape we expect to find more lysophosphatidylcholine (LPC) and less phosphatidylethanolamine (PE) in the membrane of LD compared to the ER.

In contrast to the well established view that PL demixing is curvature-dependent, we here argue the converse, i.e. that the demixing of a lipid membrane supports the generation of membrane curvature. We use yeast LD as an example and present calculations based on the standard model of LD formation. They reveal that due to lipid demixing, the PL monolayer is able to gain energy during its shape transition, thus supporting LD formation. Additionally, we show that depending on its volume and the curvature of its surface, a nascent LD is prevented from budding-off through a demixing-controlled energy barrier, whose height decreases with increasing LD volume. We predict that at a LD diameter of about 12 nm, this barrier completely vanishes and the LD is released from the ER. We thus address two essential questions (Murphy and Vance, 1999): How do nascent LD bud-off from membranes? and How is the mature size of LD determined?

2. Theoretical model

To study local deformations in an extended lipid monolayer we use the Helfrich Hamiltonian (Helfrich, 1973),

$$U=\int_{\mathcal{A}}\mathrm{d}A\left\{\frac{k_c}{2}[H(\boldsymbol{r})-2c_0]^2+\overline{k_c}K(\boldsymbol{r})\right\}, \tag{1}$$

which relates the local, total and Gaussian curvature, $H=c_1+c_2$, and $K=c_1c_2$, respectively, of a 2-dimensional surface, $\mathcal{A}$, to its elastic energy, U. Here, c_1 and c_2 denote the two principal curvatures at any given point $\boldsymbol{r}$ on the surface. The thin lipid membrane is characterized by its spontaneous curvature, c_0, and its mean and Gaussian bending modulus, k_c, and $\overline{k_c}$, respectively.

Eq. (1) describes a continuous membrane, without any reference to its internal structure. However, to be able to model a mixed membrane (i.e. a membrane consisting of various different types of PL) we assume that (1) is valid not only for a monolayer as a whole but also for every single PL molecule. Thus,

$$U_i(\boldsymbol{r})=A_{\mathrm{p},i}\left\{\frac{k_{\mathrm{c},i}}{2}[H(\boldsymbol{r})-2c_{0,i}]^2+\overline{k_{\mathrm{c}}}_{,i}K(\boldsymbol{r})\right\}, \tag{2}$$

denotes the potential energy of a single lipid where the index i distinguishes between the different types of PLs (PE, LPC, …, see below). In this equation we have assumed that across each molecule's headgroup area the change in the local membrane curvature is so small, that the integration in (1) simplifies to a multiplication with the pivotal area, $A_{\mathrm{p},i}$, occupied by a lipid of type i. The pivotal area of lipid, $A_{\mathrm{p},i}$, is defined as the area that remains unchanged in its size upon spherical bending (Rand et al., 1990). (See Fig. 3 for an illustration.) Note that in writing (2) we disregard contributions due to orientational ordering (Kralj-Iglic et al., 2002), and implicitly assume properly aligned lipids.

We may construct the PL monolayer's average free Gibbs energy, G, per lipid as the sum of independent, single molecule energies, U_i, plus their corresponding configuration entropies, i.e.

$$g:=G/N=\frac{1}{\mathcal{A}}\int_{\mathcal{A}}\mathrm{d}A\sum_{i=1}^{n}[x_iU_i(\boldsymbol{r})+x_ik_BT\ln x_i], \tag{3}$$

with, x_i, the local lipid mole fraction in the membrane; n, the number of lipid species in the monolayer; and, N, the total number of lipids. In the special case of a planar membrane $(H\to0,K\to0)$ g approaches

$$g_{\mathrm{p}}=\sum_{i=1}^{n}x_{\mathrm{p},i}\mu_{\mathrm{p},i},\quad \mu_{\mathrm{p},i}=2k_{\mathrm{c},i}c_{0,i}^2+k_BT\ln x_{\mathrm{p},i}, \tag{4}$$

where we have used $x_{\mathrm{p},i}$ and $\mu_{\mathrm{p},i}$ to denote the mole fraction and chemical potential of a flat membrane, respectively.

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