The Cirque du Soleil of Golgi membrane dynamics

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The role of lipid metabolic enzymes in Golgi membrane remodeling is a subject of intense interest. Now, in this issue, Schmidt and Brown (2009. J. Cell Biol. doi:10.1083/jcb.200904147) report that lysophosphatidic acid–specific acyltransferase, LPAAT3, contributes to Golgi membrane dynamics by suppressing tubule formation.

Phospholipase A2 (PLA2) hydrolyzes the acyl chain from the sn-2 position of a glycerolipid molecule and, in doing so, generates a molecule with a glycerol backbone esterified to a fatty acid at sn-1 and to the headgroup at sn-3. This lyso-lipid exhibits a small axial area for the acyl chain region (and is shaped as an inverted cone that promotes positive membrane curvature). What LPAATs do is re-acylate the sn-2 position with a second fatty acid (or more accurately, a fatty acyl-CoA with release of CoA as product), often an unsaturated one in higher eukaryotes, so that the axial area of the acyl chain region is much increased. When the headgroup of the glycerolipid is small, as is the case with PtdOH and DAG, the renovated glycerolipid molecule now assumes a cone shape that promotes negative membrane curvature. The general deacylation/reacylation cycle driven by sequential PLA2/LPAAT actions of this sort is termed the Lands cycle (Fig. 1; Lands and Hart, 1965). Although originally discovered as a metabolic pathway for phospholipid acyl chain remodeling in liver, the Lands cycle now resurfaces as a mechanism for controlling mammalian Golgi membrane dynamics.

LPAATs have been studied previously from the perspective of the enzymology of lipid metabolism, but their functions from the cell biological point of view remain poorly understood. The human genome sequence database identifies nine potential LPAATs (Leung, 2001; Shindou and Shimizu, 2009). A functional involvement of the Lands cycle (and LPAATs) with the Golgi complex was initially forecast by pharmacological studies with PLA2 and LPAAT inhibitors—the former interferes with various membrane trafficking pathways and the latter promoting others (de Figueiredo et al., 1998, 2000; Drecktrah et al., 2003; Chambers et al., 2005). Unfortunately, inhibitor studies of this sort are difficult to interpret. For instance, do the pleiotropic effects of the drugs report inhibition of multiple enzyme isoforms with various execution points, or are these reflections of “off-target” effects?

Schmidt and Brown (2009) now report the integral membrane protein LPAAT3 localizes to ER/Golgi membranes and exhibits lyso-PtdOH acyltransferase activity. Modulation of LPAAT3 expression has significant consequences for Golgi organization and function. siRNA-mediated silencing of LPAAT3 expression resulted in Golgi fragmentation into mini-stacks, an exquisite sensitivity of Golgi integrity to brefeldin A (BFA), and...
Figure 1. **The Lands cycle.** PLA₂ hydrolyzes the acyl-chain from a glycerophospholipid to generate a free fatty acid and a lysophospholipid product. Reacylation of lysophospholipid back to a glycerophospholipid (often with a different acyl chain at sn-2) is catalyzed by an LPAAT and involves consumption of a fatty acyl-CoA. This figure was adapted from Figure 5 in Shimizu (2009).

- Elevated mis-localization of Golgi resident proteins to the ER. Reciprocally, elevated LPAAT3 expression retards Golgi collapse into the ER upon BFA challenge. These various effects correlate with enhanced formation of Golgi-derived tubules in the face of LPAAT3 inhibitors (lyso-PtdOH formation favored) and depressed tubule biogenesis when LPAAT3 activity is increased (conversion of lyso-PtdOH to PtdOH favored). Tubulation is clearly relevant to membrane transport, as enhancement can (in specific cases) accelerate rates of cargo trafficking. Interference with tubule biogenesis, or maintenance, retards trafficking from the Golgi complex, and both anterograde and retrograde trafficking pathways are affected (Schmidt and Brown, 2009).

- The simple physical principle that connects the Lands cycle to tubulation is that production of inverted cone lyso-PtdCho by a PLA₂ strongly promotes positive membrane curvature and tubulation, whereas LPAAT3-mediated reacylation of lyso-PtdOH to PtdOH has the opposite effect (Fig. 2). Curvature parameters have been measured for lyso-PtdOH and PtdOH at physiological salt and pH concentrations, and the respective spontaneous radii of curvatures are +20Å and −46Å, respectively (for oleoyl molecular species; Kooijman et al., 2005). Interestingly, the measurements for lyso-PtdOH yield among the highest positive curvature values recorded to date. One testable question for future investigation is whether the PtdOH molecular species generated in Golgi membranes by LPAAT3 differ from those of bulk Golgi membrane PtdOH; that is, whether reacylation generates PtdOH molecular species with distinct properties such as unsaturated acyl chains at sn-2. Such a result would forecast an acyl-chain preference for LPAAT3 and the resultant molecular species would assume more extreme cone shapes that may contribute to the membrane transformations that accompany fission processes (Burger, 2000; Kooijman et al., 2005). It is also possible that newly remodeled PtdOH is a precursor for DAG, which may be the operative fission-ogenic glycerolipid. DAG assumes even more extreme negative curvatures than does PtdOH, and it is not subject to electrostatic penalties associated with packing the highly negatively charged PtdOH headgroup. Critical roles for DAG in Golgi membrane trafficking are well established (Kearns et al., 1997; Baron and Malhotra, 2002; Fernandez-Ulibarri et al., 2007; Asp et al., 2009).

- How may proteins interface with the Lands cycle in the Golgi system? Do proteins provide the primary driving force for membrane deformation, or is lipid metabolism the major factor? It is unlikely to be solely the latter—at least in this case. Simple activity of PLA₂ in generating lyso-PtdOH (or other lysolipids) is insufficient to impose significant positive curvature to membranes. The liberated fatty acid product will promote negative curvature thereby countering the effects of the lyso-lipid. Enrichment of lyso-lipid into domains is a prerequisite for membrane deformation, and such enrichment can be reinforced by proteins in several ways. First, protein domains that bend membranes (e.g., BAR domains) could bind lyso-lipids by virtue of their shape characteristics and thereby consolidate them into positively curved domains (Fig. 2). Second, coat or motor proteins that mechanically generate tubules could drive a physical rearrangement of membrane lipids to structures that best fit their shape (Roux et al., 2005; Krauss et al., 2008; Sorre et al., 2009). In this scenario, lyso-lipids re-sort preferentially to tubules and generate a positive feedback loop for membrane deformations with positive curvature.

- Reconstituted systems for membrane deformation use metabolically inert membranes, and are deprived of the active interface between lipid metabolism, proteins, and membrane dynamics. What blind spots are inherent in such protein-driven membrane deformation assays remains to be seen, but it will prove increasingly true that diverse pathways of lipid metabolism,
including the Lands cycle, lubricate the actions of proteins in productive membrane deformation pathways. Which is more important—proteins or lipids—in this arena? Let’s call it an equal-opportunity collaboration.

Given the intense interest concerning interfaces of lipid metabolism and Golgi function, it is difficult to believe that the concept of lipid metabolism as an active participant in membrane trafficking was ignored during the halcyon days when proteins involved in vesicle biogenesis were being discovered. Since the first demonstrations that specific lipid metabolic pathways are central to these processes (Bankaitis et al., 1990; Cleves et al., 1991), work from numerous laboratories has greatly expanded the lipid–Golgi interface. The report of Schmidt and Brown (2009) adds new sets of activities to the ever-growing roster of lipid metabolic enzymes whose actions contribute to the remarkable Cirque du Soleil of Golgi membrane dynamics. Indeed, we may soon wonder whether there is any such thing as a simple “housekeeping” lipid metabolic pathway in eukaryotic cells.

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References


