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Modulation of endomembranes morphodynamics in the secretory/retrograde pathways depends on lipid diversity

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Membrane lipids are crucial bricks for cell and organelle compartmentalization and their physical properties and interactions with other membrane partners (lipids or proteins) reveal lipids as key actors of the regulation of membrane morphodynamics in many cellular functions and especially in the secretory/retrograde pathways. Studies on membrane models have indicated diverse mechanisms by which membranes bend. Moreover, *in vivo* studies also indicate that membrane curvature can play crucial roles in the regulation of endomembrane morphodynamics, organelle morphology and transport vesicle formation. A role for enzymes of lipid metabolism and lipid–protein interactions will be discussed as crucial mechanisms in the regulation of membrane morphodynamics in the secretory/retrograde pathways.

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Introduction

Membrane lipids have a well known crucial function in cell and organelle compartmentalization. Through interactions of lipids with membrane proteins, lipids play an important function in regulating membrane protein activities. Numerous data demonstrate lipids being involved in signaling processes and being key actors to regulate membrane dynamics in many physiological functions. For example galactolipids, which represent up to 75% of thylakoid lipids, are crucial for thylakoid ultra-structure and photosynthesis efficiency [1]. Cardiolipin, a specific mitochondrial lipid, is essential for mitochondrial morphogenesis, ultra-structure and function [2,3], and its properties make it crucial for mitochondrial fission [3]. Another example is given by the important role of polyphosphoinositides and their corresponding phosphatases in vacuolar functioning and morphology in plant cells [4].

Similarly, eukaryotic secretory/retrograde pathways are also tremendously regulated by the physicochemical properties of membrane lipids [5–8]. In all eukaryotic cells the establishment, maintenance and plasticity of the morphology of organelles is fundamental to their function. Several families of proteins are involved in shaping organelle morphologies [9–11] as exemplified in plants by the reticulons and the atlastin homologue proteins [12,13]. Beside proteins, lipids and enzymes of their metabolism are largely involved in governing the complex mechanisms of membrane dynamics and their regulation in the secretory/retrograde pathways.

Physical properties of lipids impact membrane curvature

Studies on membrane models have unraveled many mechanisms by which membranes can bend. Membrane curvature is essential for ER structure and ER exit sites organization and localization at the ER [14,15•]. On the protein side, the asymmetric insertion of a protein into a membrane bilayer, the adhesion of a curved protein domain to the membrane surface, the assembly of protein scaffold and membrane protein crowding through protein–protein interactions can be driving forces for membrane curvature and bending [10,11], and the energy cost these forces required has been deeply analyzed [11]. On the lipid side, it has been detailed how diverse lipids can induce membrane curvature [16]. As indicated in Table 1, each lipid can be characterized by a packing parameter (P) where $P = v/a.l$ and v corresponds to the molecular volume, a is related to the cross-sectional area of the head group and l is the length of the molecule [16]. P indicates whether the lipid has the tendency to induce a positive or negative membrane curvature. Most of the roles of specific proteins and lipids in regulating membrane curvature were determined on membrane models and therefore we have to be aware that their implication would have to be also evaluated in membranes where physiological conditions are met [10]. Although it is clear that membrane curvature is playing crucial roles in the regulation of endomembrane morphodynamics, possible discrepancies between *in vitro* and *in vivo* systems have definitely not to be underestimated [7].

Table 1

Relationship between lipid physical properties, enzymes of lipid metabolism and endomembrane morphodynamics in the secretory/endocytic pathways of plant cells and other eukaryotic cells.

Lipids		Enzymes and types of actions	Effect on endomembranes
Lipids: $P > 1$ (cone-shaped, negative membrane curvature)	DAG	DAG kinases, PA phosphatases, inhibition of phospholipid metabolism	- DAG increase induces Golgi vesiculation. - DAG decrease inhibits Golgi budding. [7,27]
	FFA	Activation of PLA2	Increase of membrane permeability. [20]
	LCB	Inhibition of ceramide synthases	LCB increase induces ER morphological changes. [***36***]#
	PA	Activation of phospholipase D	- PA increase induces Golgi vesiculation. - PA decrease inhibits Golgi budding. [18,19••,***22–26***]#
	Sterols	Enzymes of sterol metabolism	- Sterol increase induces Golgi vesiculation. - Sterol decrease inhibits Golgi budding. [5,7]
Lipids: $P < 1$ (inverted cone-shaped, positive membrane curvature)	lysoPL (LPA, LPC)	Activation of phospholipase A1, PLA2, Inhibition of lysoPL acyltransferases	- Increase of permeability. - LPC increase induces ER-Golgi tubulation. - Inhibition of LPA acylation disadvantages Golgi budding. [18,19••,***22–26***]#
	PIP	PI kinases, Phosphoinositide phosphatases	Regulation of membrane budding and trafficking. [***49,50•,51•,52••,53***]#
	PIP2	PIP kinases, Phosphoinositide phosphatases	Regulation of membrane budding and trafficking. [***49,50•,51•,52••,53***]#

DAG: diacylglycerol; ER: endoplasmic reticulum; FFA: free fatty acids; LCB: Long chain bases; LPA: lysophosphatidic acid; LPC: lysophosphatidylcholine; lysoPL: lysophospholipids; PA: phosphatidic acid; PLA2: phospholipase A2 which hydrolyzes major phospholipids at the sn2 position; PIP: phosphatidylinositol phosphate; PIP2: phosphatidylinositol diphosphate. P (packing parameter) = v/al: v corresponds to the molecular volume, a is related to the cross-sectional area of the head group and l is the length of the lipid molecule [16]. Types of actions on concerned enzymes: either genetic and/or pharmacological approaches were considered. A caution must be highlighted here for all lipids: their effects can be linked either to their biophysical properties, their potential signaling roles or both.

[#] References in italic and bold are concerning plant data.

A role for the Lands cycle and related enzymes in membrane morphodynamics?

The Lands cycle involves phospholipases A$_2$ (PLA$_2$) and lysophospholipid acyltransferases (LPAT) to govern fatty acyl remodeling of phospholipids synthesized through the Kennedy pathway [17,18]. PLA$_2$ form lysophospholipids (inverted cone-shaped) that have the propensy to induce local positive membrane curvature (Table 1, Figure 1) and LPAT produce phospholipids with properties that vary depending on the size of their polar head and the unsaturation of their fatty acids. Phospholipids with a small polar head (phosphatidic acid: PA, Table 1; but also phosphatidylethanolamine: PE and phosphatidylserine: PS) can induce negative membrane curvature and favors non-lamellar phases which are known to be involved in membrane fusion/fission processes whereas phosphatidylcholine (PC) which is more cylindrical, either stabilizes the bilayer leaflet or slightly induces a negative membrane curvature when its fatty acids are highly unsaturated. All these activities may therefore regulate the local dynamic state of endomembranes. The pioneering work of Brown and colleagues in animal cells [18] has paved the way to unravel the role of such activities in regulating the dynamics of the Golgi and the emission of Golgi-derived COPI vesicles but also that of ER-derived COPII vesicles [(18, Figure 1)]. The best example in animal cells is the regulation of COPI vesicle versus tubule formation from the Golgi [19••]. COPI buds are elongated to form tubules through the activity of cPLA$_2$ which produces lysophosphatidic acid (LPA)/lysophosphatidylcholine (LPC) (positive membrane curvature). Contrastingly, LPA acyltransferase and PLD activities which produce PA (negative membrane curvature) govern vesicle formation and fission [19••]. The PLA$_2$ is also producing free fatty acid (FFA, negative membrane curvature) which could in theory counteract the effect of LPA/LPC although this is not very likely due to that FFA are diffusing more rapidly than lysophospholipids from one leaflet to the other one [20]. Therefore lysophospholipids are likely to be more concentrated in one of the two leaflets compared to FFA, and that would induce a dynamic asymmetry which helps membrane bending. Such a regulation of vesicles/tubules formation may be a way to control the anterograde and retrograde trafficking within the Golgi complex and towards the ER in animal cells. Very recently, using very high speed and high resolution confocal microscopy, a new model was proposed in yeast where *cis*-Golgi recovers material from ER export sites via specific contacts [21••]. One can easily imagine that specific enzymes of lipid metabolism such as those shown in Figure 1 could be involved in the fusion events associated to the 'hug-and-kiss' process proposed between *cis*-Golgi membranes and the ER export sites in yeast [21••].

In plant cells, only very few investigations approached these concepts. Pharmacological and genetic approaches suggested that inhibition of PLA$_2$α impairs PIN protein trafficking in root cells and showed an accumulation of