diffusional rates are significantly higher than those determined for plasma membrane proteins[33]. While much remains to be learned of the mechanisms of Golgi membrane organization and dynamics, the discovery of novel links with the cytoskeleton has given us new possibilities to consider in the next century of research on this organelle.

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Lipids of the Golgi membrane

Gerrit van Meer

The thin membrane of the endoplasmic reticulum matures into the thick plasma membrane in the Golgi apparatus. Along the way, the concentrations of cholesterol and sphingolipids increase. Here, Gerrit van Meer discusses how this phenomenon may reflect an intricate lipid–protein sorting machinery. Synthesis of sphingolipids, translocation across the Golgi membrane and lateral segregation into lumenal domains seem to be key events. In addition, signalling lipids indicate the lipid status of the Golgi and interact with proteins of the transport machinery to regulate membrane flux.

The membranes of the mammalian Golgi complex contain a mix of lipids similar to that of other organelles. The most abundant phospholipid is phosphatidylcholine (PtdCho), followed by phosphatidylethanolamine (PtdEtn), phosphatidylserine (PtdSer), phosphatidylinositol (PtdIns) and the sphingophospholipid sphingomyelin (SM). The Golgi membrane also contains cholesterol and glycosphingolipids (Fig. 1). Plant and yeast cells contain other sterols and sphingolipids based on inositolphosphoceramide (InsPCer; see Ref. 1). The Golgi is intermediate between endoplasmic reticulum (ER) and plasma membrane in terms of lipid composition (Table 1). Morphological and biochemical studies have suggested that there is a gradual increase in the concentration of SM and cholesterol from the *cis* to the *trans* Golgi[2,3]. It is difficult to determine the Golgi content of diacylglycerol (DAG), ceramide, free fatty acids and lysophospholipids as these can be produced by phospholipases during membrane purification.

Lipid synthesis and transbilayer orientation

Glycerophospholipids and sterols are synthesized mainly in ER, mitochondria and peroxisomes. By contrast, most sphingolipid synthesis occurs in the Golgi. Ceramide is made in the ER (although it is unclear where dihydroceramide desaturase introduces the double bond in sphingosine[4]) and is used by all mammalian cells to produce SM and glucosylceramide (GlcCer), the precursor for the higher glycolipids. SM (and DAG) are synthesized on the lumenal surface of the *cis* and *medial* Golgi from PtdCho and ceramide (Fig. 2)[5,6]. The yeast equivalent of SM, InsPCer, is made in the ER. In the yeast Golgi, DAG is produced when a second InsP is transferred from PtdIns to mannosyl-InsPCer to yield mannosyl$(InsP)_2$Cer (Ref. 1). DAG and ceramide are signalling lipids (see below), making the enzymes of sphingophospholipid synthesis prime candidates for regulation.

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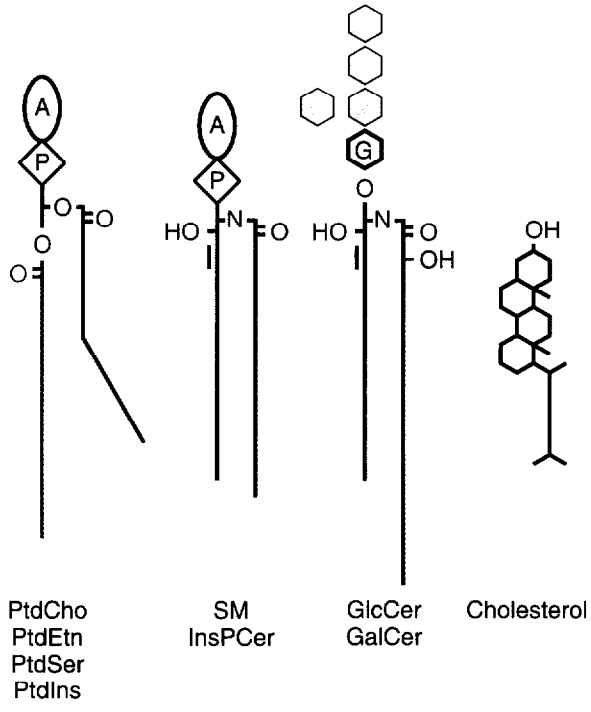

FIGURE 1

Schematic structure of the major lipids of the Golgi membrane. The backbones of the various molecules are in red: glycerol in the diacylglycerol (DAG) of glycerophospholipids, sphingosine in the ceramide of sphingophospholipids and glycosphingolipids, and cholesterol. The green fatty acid on the glycerol is generally a saturated chain of 16 or 18 carbon atoms (C16:0, C18:0), while the blue fatty acid is usually unsaturated (C18:1, C18:2 or C20:4) in phosphatidylcholine (PtdCho), phosphatidylethanolamine (PtdEtn), phosphatidylserine (PtdSer) and phosphatidylinositol (PtdIns), saturated (C18:0) in sphingomyelin (SM), and saturated and long (C20:0–C26:0) in inositolphosphoceramide (InsPCer) and in glycolipids. The phospholipid headgroup (black) consists of phosphate (P) and an alcohol (A), choline in PtdCho and SM, ethanolamine in PtdEtn, serine in PtdSer and inositol in PtdIns and InsPCer; 'A' is absent in phosphatidic acid and in ceramide phosphate, while lysophosphatidic acid and sphingosine phosphate in addition lack the blue fatty acid. Most complex glycolipids are synthesized from glucosylceramide (GlcCer) by stepwise addition of sugars (yellow hexagons) to the glucose (G) headgroup (black hexagon). 'G' is galactose in galactosylceramide (GalCer). In 50% of GalCer, the acyl chain is hydroxylated in position 2. This –OH (black in figure), with the –OH in the sphingosine (and in the carbohydrates of the glycolipids) and the –NH– in the amide bond, contributes to the hydrogen-bonding capacity of sphingolipids. Similarly, the hydroxyl at carbon 3 of cholesterol can partition in hydrogen bonding with SM but most likely not glycerophospholipids[23]. Its β orientation is required for biological activity. Cholesterol (like yeast ergosterol) has a rigid planar steroid ring structure with the –OH, methyl groups and side chain all located towards the same side of the plane.

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The gene encoding UDP-glucose:ceramide glucosyltransferase (CGlcT), which catalyses the synthesis of GlcCer, has been cloned[7]. CGlcT has been localized by cell fractionation to *cis/medial* Golgi, where it probably competes with SM synthase for ceramide. Part of the activity might also reside in *pre* Golgi or *trans* Golgi compartments[8,9]. GlcCer is synthesized on the cytosolic surface of the membrane. By an unknown mechanism, it can translocate to the lumen where it can be trapped by galactosylation to lactosylceramide (LacCer, Fig. 2)[10,11]. Transferases in the Golgi lumen generate a specific series of complex glycolipids from LacCer by stepwise addition of carbohydrates. The transferases often compete for common substrates such as LacCer[12] or the ganglioside NeuAc-LacCer[13] and activated sugars. The previous assignment of early transferases to the *cis* Golgi and of late transferases to the *trans* Golgi (see Ref. 14) is not supported by recent immunoelectronmicroscopic evidence that the late enzyme *N*-acetylgalactosaminyltransferase is present throughout the Golgi[14] and the finding that the early UDP-galactose:GlcCer galactosyltransferase, GlcCer-GalT (Fig. 2), copurifies with *trans* Golgi markers[15].

Galactosylceramide (GalCer) is synthesized in the ER of myelinating cells and some epithelial cells by UDP-galactose:ceramide galactosyltransferase (CGalT). Besides the CGalT activity in the ER, we and others observed a CGalT activity in the Golgi *in vitro*[11], but experiments where the gene encoding CGlcT was transfected into CGalT- and CGlcT-negative cells demonstrated that this was due to activity of CGlcT in the absence of UDP-Glc (H. Sprong, B. Kruithof, R. Leijendekker, J. W. Slot, G. van Meer and P. van der Sluijs, unpublished). CGalT does not scavenge all the ceramide in the ER because it has a preference for ceramide with a 2-hydroxy fatty acid, which only seems to occur in cell types expressing CGalT. GalCer synthesized in the ER lumen has access to the cytosolic surface[11], suggesting that GlcCer and GalCer could have functions on the cytosolic face of cellular membranes. GalCer can be galactosylated and/or sulfated (or sialylated) in the Golgi lumen. These products cannot translocate to the cytosolic face.

Lipid transport

All models of intra-Golgi membrane traffic invoke transient membrane continuities and contain an anterograde and retrograde component[16,17]. In principle, therefore, Golgi membrane lipids can equilibrate between the various Golgi membranes. Net transfer of lipids from the ER to the plasma membrane occurs when more membrane area enters the *cis* Golgi than recycles to the ER and when more membrane leaves the TGN than returns by recycling.

In addition, lipids that reside in the cytosolic leaflet of Golgi membranes can potentially desorb from the membrane into the cytosol and transfer to other membranes by monomeric diffusion. Net transfer occurs when membranes have different affinities for a lipid or in the presence of a metabolic trap. Transfer of lipids with two long chains and of cholesterol occurs with a half-time of hours but can be accelerated by lipid transfer proteins (LTPs). At present, three types of LTPs seem most relevant for intracellular lipid traffic, the PtdCho-TP, the various PtdIns-TPs[18] and the GalCer/GlcCer-TP[19]. LTPs equilibrate lipid compositions by mixing the various fatty acyl species of a lipid class or, in the case of dual-specificity LTPs, by mixing the two lipids. The rapid equilibration of newly synthesized PtdCho between cellular membranes (see Ref. 3) and the persistence of GlcCer transport to the plasma membrane in the

TABLE 1 – LIPID COMPOSITION OF MEMBRANES ALONG THE SECRETORY PATHWAY IN RAT LIVER

	PtdCho[a]	PtdEtn	PtdSer	PtdIns	SM	Glycolipids[b]	Cholesterol/phospholipid
	mol % of phospholipid						mol/mol
ER	58	22	3	10	3	+/– –	0.08
Golgi membrane[c,d]	50	20	6	12	8	+/–	0.16
Plasma membrane	39	23	9	8	16	+	0.35

[a]Data from Fleischer *et al.*[38]. Similar data have been obtained by Morré and colleagues[3,39], who also reported a dramatic increase in fatty acid saturation in the plasma membrane. While ER PtdCho and PtdSer contained 49% and 75% unsaturated fatty acids, respectively, this was reduced to 30% and 11% in the plasma membrane[39]. The gradients along the secretory pathway are generally observed, although the actual numbers vary for different cell types and depend on the techniques used[40], as is illustrated by a report[41] that actually >5 (weight)% of the phospholipid in rat liver Golgi consists of the unusual semilysobisphosphatidic acid.

[b]No accurate data are available on the glycolipid content of ER and Golgi, while it varies from several mol % of membrane lipids in regular plasma membranes to 30 mol % in the myelin membrane and the apical plasma membrane of intestinal epithelial cells.

[c]Low quantities of cholesterol esters and triacylglycerol are found in Golgi membrane preparations from liver[38,39,42]. It is unclear whether these lipids were present in the membrane proper or in remaining Golgi lipoproteins.

[d]Because the lipoproteins inside the Golgi are in close contact with the surrounding membrane, the phospholipids on the lipoprotein surface may reflect those in the lumenal leaflet of the Golgi membrane. With this assumption, it can be calculated from the composition of the lipoproteins and that of the Golgi membrane[40] that the lumenal leaflet contains 75% of the SM, 60% of the PtdIns, 56% of the PtdCho, 13% of the PtdEtn, and 11% of the PtdSer. This is roughly the phospholipid asymmetry observed in the erythrocyte plasma membrane (see Ref. 21).

Abbreviations: ER, endoplasmic reticulum; PtdCho, phosphatidylcholine; PtdEtn, phosphatidylethanolamine; PtdIns, phosphatidylinositol; PtdSer, phosphatidylserine; SM, sphingomyelin.

presence of an inhibitor of vesicular traffic, brefeldin A (Ref. 20), suggest that LTPs function in cells. Convincing evidence that they can generate net lipid transport is still lacking. However, as described below, LTPs appear to regulate membrane traffic by an independent mode of action.

Lipid sorting and lipid domains

Differences in lipid composition can be brought about by situating synthetic enzymes or hydrolases in a specific cisterna and on one side of the membrane (e.g. LacCer synthase[15]). Alternatively, differences can be generated by specificity in transport. Lipid sorting implies a change in the surface density of a particular lipid at one site as compared with another. Specific lipids can be concentrated in one leaflet of the membrane; for example, PtdSer and PtdEtn are enriched in the cytosolic leaflet of the plasma membrane by the ATP-dependent aminophospholipid translocase (see Ref. 21; Table 1). It is not clear whether this protein is active in the Golgi membrane. Similarly, it is unclear whether translocation of GlcCer and GalCer to the Golgi lumen is unidirectional (Fig. 2) and whether any other potential lipid pumps such as multidrug resistance proteins[22] are present and active in the Golgi.

Alternatively, lipids can be transported unidirectionally along with membrane proteins. Even in the absence of net transfer of bulk lipids between two membranes, net transfer of a particular lipid class can occur when this lipid is preferentially incorporated in anterograde transport, while some other lipid is then transported in a retrograde direction. This requires lateral inhomogeneity, a domain enriched in a particular lipid, at the exit site of the compartment, which would probably be generated by the lipid having an affinity for a component of the domain. SM and complex glycolipids are more abundant in the plasma membrane compared with the Golgi and in the Golgi compared with the ER (Table 1), suggesting that they are preferentially included in the anterograde route and/or excluded from retrograde transport through the Golgi. These lipids are lumenal and can only be transported on the inner aspect of vesicles or tubules. Thus, the surface density of sphingolipids must be enhanced at sites of anterograde transport and reduced at sites of retrograde vesicle budding. In an environment of glycerolipids, sphingolipids can aggregate spontaneously. In contrast to glycerolipids, they can act as donors of intermolecular hydrogen bonds (Fig. 1), resulting in denser packing especially in the presence of cholesterol[23]. Since cholesterol interacts more strongly with sphingolipids than with the cellular unsaturated glycerolipids[23], anterograde sorting of the sphingolipids provides a potential mechanism for enriching cholesterol along the secretory pathway (Table 1). Disaturated PtdSer is enriched on the cytosolic surface of the plasma membrane (Table 1). Could it be that PtdSer is enriched along the secretory pathway via domains on the cytosolic surface of the Golgi?

Sphingolipid molecules form longer cylinders than phospholipids: in the presence of cholesterol, a bilayer of the typical mammalian SM with a C18:0 acyl chain displays a transbilayer headgroup separation of 46–47Å (Ref. 24), compared with 40Å for the most abundant PtdCho, C16:0/C18:1 (Ref. 25). The differences are enhanced by the fact that glycolipids tend to have longer acyl chains than SM (Fig. 1) and that the thickness of a bilayer of C16:0/C18:1 PtdCho

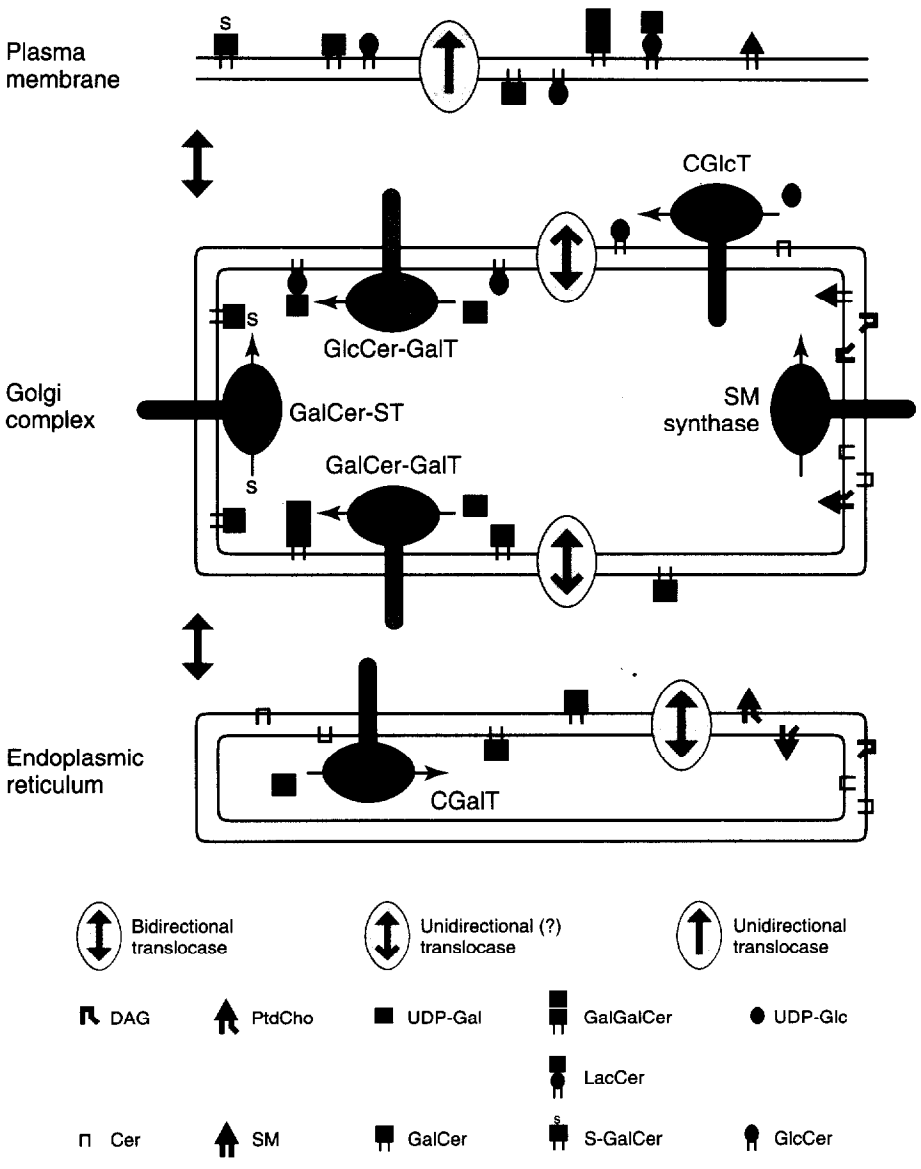

FIGURE 2

Orientation of enzymes of simple sphingolipid synthesis in the membranes of the endoplasmic reticulum (ER) and Golgi. The Golgi complex is represented as a single-membrane-bounded space. After synthesis in the ER, ceramide (Cer) can be converted to galactosylceramide (GalCer) in the ER of some cells by ceramide galactosyltransferase (CGalT). However, most ceramide is transported to the Golgi to be utilized with phosphatidylcholine (PtdCho) by sphingomyelin (SM) synthase to yield SM and diacylglycerol (DAG) on the lumenal side. Part of the ceramide is converted to glucosylceramide (GlcCer) by ceramide glucosyltransferase (CGlcT)[7] on the cytosolic face. After translocation of GlcCer to the lumenal side, it can be further glycosylated, first by GlcCer-galactosyltransferase (GlcCer-GalT) to lactosylceramide (LacCer). GalCer can be converted into di-galactosylceramide (GalGalCer) by GalCer-GalT, or into sulfate-GalCer (S-GalCer) by a sulfotransferase (ST). PtdCho and GalCer can flip freely across the ER membrane. GalCer and GlcCer can translocate towards the lumenal leaflet of the Golgi membrane. Complex glycolipids and SM do not translocate towards the cytosolic face[10,11]. Short-chain analogues of GlcCer, GalCer and SM can be translocated to the outside of the plasma membrane by multidrug transporters[22], but it is unclear whether natural lipids can. DAG and ceramide flip across membranes spontaneously.

decreases to 35Å in the absence of cholesterol[25]. An enrichment in sphingolipids and cholesterol could explain the increased thickness of the membrane of the *trans* Golgi and plasma membrane. One model for membrane protein sorting in the Golgi is that it is mediated by preferential interactions with membranes of different thicknesses depending on the length of the transmembrane domain[26].

Lipid transport data have suggested that lipid domain formation is responsible for the segregation of apical and basolateral lipids in epithelial cells[27]. Superimposed on the enrichment of sphingolipids along the anterograde pathway, glycosphingolipids are enriched over SM and PtdCho into apical precursor domains. Proteins anchored to the lumenal leaflet by a glycosyl-PtdIns tail are also directed to the apical surface, and the entry of a glycosyl-PtdIns protein and an apical transmembrane protein into the Golgi is accompanied by a reduced detergent solubility. These data have been interpreted in favour of a lipid–protein microdomain model for apical transport[28,29]. The identification of caveolin in this apical pathway has expanded the concept of glycosphingolipid microdomains to include the caveolae at the cell surface. Major questions are what lipid–protein interactions can locate the domains to specific budding sites[30] and whether the lipids on the opposite, cytosolic side of the domain (PtdSer?) display a domain organization as well. However, despite being widely acclaimed and attractive, the lipid microdomain hypothesis is supported by largely indirect evidence. The isolation of highly pure Golgi transport vesicles and microscale lipid analysis could provide a solution[31]. Our original observation, preferential apical transport of a short-chain GlcCer analogue compared with a SM[27], corresponds at least partially to an alternative process. After synthesis of the short-chain GlcCer on the cytosolic face of the Golgi, it diffuses to the plasma membrane, after which it is translocated to the outer leaflet by multidrug resistance P-glycoproteins (Ref. 22; K. N. J. Burger, R. Raggers and G. van Meer, unpublished). It must now be determined how endogenous GlcCer reaches the apical cell surface.

Signalling lipids

It has been clear for some time that lipid second messengers might signal not only at the plasma membrane but also at other cellular locations. A prime example is DAG, which, when generated at the plasma membrane, activates cytosolic protein kinases C. It was proposed ten years ago that DAG produced by SM synthase in the Golgi might also signal, and that its level would be controlled[32]. Work by Bankaitis and colleagues has substantiated this view and culminated in the conclusion that a minimal concentration of DAG in the Golgi is required for the production of secretory vesicles[1]. A *Saccharomyces cerevisiae* mutant in intra-Golgi transport, *sec14*, showed that the PtdIns/PtdCho

transfer protein (PtdIns-TP) is required for protein transport. From characterizing bypass mutations, the group has presented a unifying hypothesis for how PtdIns-TP, in its PtdCho- and PtdIns-bound forms, regulates enzymes involved in PtdCho and PtdIns metabolism that together determine the concentration of DAG[1].

In mammalian cells, an unrelated PtdIns-TP is Golgi associated[18] and binds to PtdIns, PtdCho and also SM. By analogy to yeast, the SM-bound form could regulate DAG levels through SM metabolism. An interesting candidate for regulation is SM synthase (the gene has not been cloned yet), which produces DAG and utilizes ceramide. Ceramide appears to oppose DAG and inhibit protein traffic through the Golgi[33]. This type of cytosolic SM 'sensor' fits the idea of a regulatory SM pool in the cytosolic leaflet of the plasma membrane[34,35]. It remains unclear what would be the origin of this SM pool since SM is synthesized on the lumenal side and does not translocate (Fig. 2). One model for the regulation of membrane traffic by DAG and ceramide is that DAG activates Golgi DAG-dependent protein kinases C, which in turn activate phospholipase D to make phosphatidic acid (PtdOH; see Ref. 36). This PtdOH is thought to play a role in Golgi coated-vesicle formation, whereas PtdOH generated from DAG appears inactive (see Ref. 1). Ceramide could inhibit phospholipase D, which, like other proteins, is regulated by PtdIns (4,5)-bisphosphate[36]. Phosphoinositide 3-kinase is essential for a number of steps in post-Golgi membrane traffic, another example of the role of the various phosphoinositides in membrane traffic[37].

In conclusion

A striking property of the mammalian Golgi is that it is the site of most sphingolipid synthesis. Apparently, GlcCer, GalCer and SM occur to some extent on the cytosolic surface of the Golgi. They can interact with cytosolic LTPs, which are potentially involved in regulating Golgi levels of DAG and ceramide, lipids that in turn regulate flux through the Golgi most likely through a second layer of signalling lipids, PtdOH and phosphoinositides. However, the bulk of the sphingolipids are thought to reside on the lumenal face of the Golgi membrane, where most of them are synthesized. There, they apparently self-aggregate into lumenal domains. If, as expected, domains play a role in preferential transport of the sphingolipids and cholesterol in the anterograde direction, they must be situated at sites of vesicle budding. This is also true for the PtdOH and the phosphoinositides involved in vesicle budding. With sphingolipid domains and signalling lipids on opposite sides of the budding membrane, it is appealing to think that they might be organized in a membrane-spanning lipid–protein complex, where there could even be a role for local lipid translocators. However, before getting carried away by these exciting possibilities, we had better obtain direct evidence for the existence of lipid domains in the Golgi and collect more data on lateral and transverse lipid–protein interactions in the membrane.

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