

Activation of ADP-ribosylation Factor 1 GTPase-Activating Protein by Phosphatidylcholine-derived Diacylglycerols*

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Disassembly of the coatmer from Golgi vesicles requires that the small GTP-binding protein ADP-ribosylation factor 1 (ARF1) hydrolyzes its bound GTP by the action of a GTPase-activating protein. *In vitro*, the binding of the ARF1 GTPase-activating protein to lipid vesicles and its activity on membrane-bound ARF1_{GTP} are increased by diacylglycerols with monounsaturated acyl chains, such as those arising *in vivo* as secondary products from the hydrolysis of phosphatidylcholine by ARF-activated phospholipase D. Thus, the phospholipase D pathway may provide a feedback mechanism that promotes GTP hydrolysis on ARF1 and the consequent uncoating of vesicles.

In the early secretory system, rounds of vesicle budding and fusion are linked to the GTPase cycle of the small G protein ARF1.¹ Following a GDP to GTP exchange catalyzed by a guanine nucleotide exchange factor, ARF1_{GTP} tightly associates with the Golgi membrane and triggers the assembly of a coat protein complex termed coatmer (1). These events result in the budding of a transport vesicle. The subsequent hydrolysis of ARF1-bound GTP triggers vesicle uncoating, a prerequisite for vesicle fusion (2, 3). This process is catalyzed by an ARF1 GTPase-activating protein (GAP) (4). Lipids appear to play a critical regulatory role in vesicular transport. At the Golgi, ARF1 activates a PLD (5, 6), which converts phosphatidylcholine (PC) to phosphatidic acid (PA), an event that has been proposed to contribute, at least in part, to the recruitment of coatmer (7). Both PLD (8) and a recently described ARF1 exchange protein named ARNO (9) are activated by phosphatidylinositol 4,5-bisphosphate (PIP₂).

In the GTP state, ARF1 is attached to vesicles through the insertion of its myristate and of hydrophobic residues of its N-terminal amphipathic helix in the membrane lipids and through electrostatic interaction between basic residues and the polar head of acidic lipids, without specificity for phosphatidylserine (PS), phosphatidylglycerol, PA or even Pip₂ (10). The membrane attachment of ARF1_{GTP} implies that catalysis of GTP hydrolysis by ARF1 GAP occurs at the membrane surface.

Here, we show that the membrane binding of ARF1 GAP and its activity on ARF1_{GTP} are dramatically increased by diacylglycerols with monounsaturated acyl chains.

EXPERIMENTAL PROCEDURES

Materials—All lipids were of the highest available purity (>98%). Brain PA, egg PC, egg phosphatidylethanolamine (PE), brain PS, and brain PIP₂ were obtained from Sigma. Synthetic lipids were obtained from Sigma except for 1-palmitoyl-2-oleoyl-*sn*-glycerol and 1-stearoyl-2-oleoyl-*sn*-phosphatidylcholine, which were obtained from Avanti Polar Lipids (Birmingham, AL).

Vesicles—Unilamellar vesicles were prepared by the extrusion method as described previously (9, 10). Briefly, solutions of lipids in chloroform:methanol or, in the case of PIP₂, in chloroform:methanol:H₂O:1 N HCl (20:9:1:0.1) were mixed in the required proportion. A film was formed from the lipid mixture in a rotary evaporator and resuspended in 50 mM Hepes, pH 7.5, and 100 mM KCl. The suspension was vortexed for 20 min and then freeze-thawed 5 times. Unilamellar vesicles were produced by extrusion through a 0.1- μ m pore size polycarbonate filter (isopore, Millipore) using an extrusion apparatus. For sucrose-loaded vesicles, the same procedure was used except that the buffer was 220 mM sucrose, 20 mM Tris, pH 7.5, and that 0.4- μ m pore size polycarbonate filters were used. After extrusion, the sucrose-loaded vesicles were diluted 1:5 in 20 mM Tris, pH 7.5, and 120 mM NaCl, centrifuged for 10 min at 400,000 $\times g$, and resuspended in the same buffer before use.

Protein Purification—¹⁻²⁵⁷GAP, the longest form of ARF1 GAP that can be expressed in *Escherichia coli*, and the full-length yeast homolog Gcs1 were expressed in BL21 *E. coli* with an N-terminal hexahistidine tag (4, 11). Proteins were solubilized from inclusion bodies in 6 M guanidine, 20 mM Tris, 100 mM sodium phosphate pH 8. After centrifugation, the supernatant was mixed with Ni-NTA beads and stirred for 45 min. The beads were washed with the same guanidine solution, transferred to a column, and then washed with 6 M guanidine, 100 mM sodium phosphate, pH 6.3. Proteins were eluted with the same solution supplemented with 0.5 M imidazole. After addition of 5 mM dithiothreitol, proteins were dialyzed overnight against 25 mM Tris, pH 7.5, 50 mM NaCl, and 2 mM dithiothreitol. ¹⁻²⁵⁷GAP was further purified by Mono Q chromatography using a NaCl gradient in 25 mM Tris, pH 7.5. ¹⁻²⁵⁷GAP and Gcs1 were stored at -20 °C with 33% glycerol. As judged by SDS-polyacrylamide gel electrophoresis, ARF1 GAP and Gcs1 were 80% pure. Recombinant ARNO and myristoylated ARF1 were purified as described (9, 12).

Fluorescence Measurements—ARF1_{GTP} shows an intrinsic fluorescence that is 3 times as high as ARF1_{GDP} (10). This difference was used to monitor in real time ARF1 activation upon GDP to GTP exchange and ARF1 deactivation upon GTP hydrolysis. All measurements were performed at 37 °C in 50 mM Hepes, pH 7.5, 100 mM KCl, 1 mM MgCl₂, and 2 mM dithiothreitol and with unilamellar vesicles (final lipid concentration, 250–500 μ M).

Sedimentation Assay—¹⁻²⁵⁷GAP (1.5 μ M) or Gcs1 (1 μ M) was incubated at room temperature in 20 mM Tris, pH 7.5, 120 mM NaCl, 1 mM MgCl₂, and 2 mM dithiothreitol with sucrose-loaded vesicles (final lipid concentration, 2.5 mM). After centrifugation (400,000 $\times g$, 15 min), the relative amounts of protein in the supernatant and the pellet were determined by densitometry of SDS-polyacrylamide gel electrophoresis after Coomassie Blue staining. It must be noted that the lipid pellet includes a small but significant volume of external solution and therefore traps about 2% of any soluble protein. Therefore, only values of membrane binding >5% are significant.

Data Analysis—The kinetics of GAP-catalyzed GTP hydrolysis on

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¹ The abbreviations used are: ARF1, ADP-ribosylation factor 1; GAP, GTPase-activating protein; PLD, phospholipase D; DAG, diacylglycerol; DOG, dioleoylglycerol; PA, phosphatidic acid; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PS, phosphatidylserine; PIP₂, phosphatidylinositol 4,5-bisphosphate; NTA, nitrilotriacetic acid.

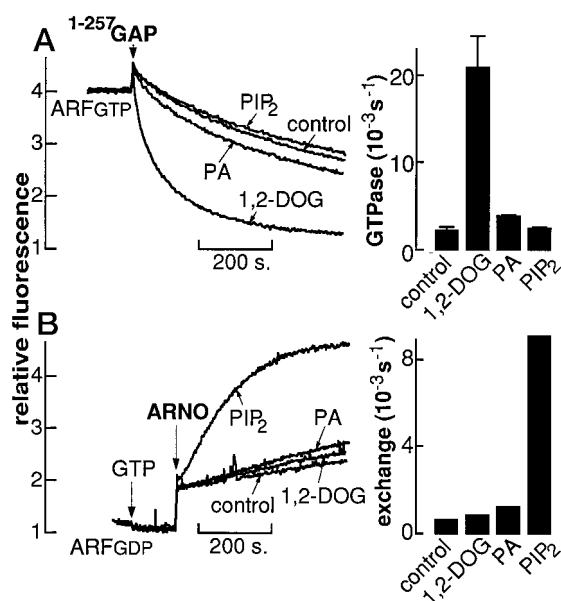


FIG. 1. Stimulation of ARF1 GAP activity by 1,2-DOG. *A*, time course of $1-257$ GAP-catalyzed hydrolysis of GTP on ARF1 with vesicles containing 30% bovine brain PS and, where indicated, 5% bovine brain PIP₂, 10% egg PA, or 10% 1,2-DOG. The remaining lipid was egg PC. In a preliminary stage, myristoylated ARF1_{GDP} (0.2 μ M) was mixed with vesicles (total lipid concentration, 325 μ M) and converted to the high fluorescence GTP state by the addition of 40 μ M GTP (or GTP γ S) and by chelating magnesium with EDTA (9, 11). In a second stage, the concentration of magnesium was restored to 1 mM, and 40 nM $1-257$ GAP was added. GTP hydrolysis on ARF is seen by a large decrease in ARF fluorescence, the amplitude of which corresponds to the previous GTP binding signal. *B*, effect of PIP₂, PA, and 1,2-DOG on the catalysis of ARF activation by ARNO, the nucleotide exchange factor of ARF1. Myristoylated ARF1_{GDP} (0.2 μ M) was incubated with vesicles of the same composition as in *A* and, at the time indicated, GTP (40 μ M) and ARNO (20 nM) were added. The right panels show ARF1 GAP and ARNO activities expressed as $1/t_{1/2}$, where $t_{1/2}$ is the half-time of ARF1 deactivation or activation upon the addition of $1-257$ GAP or ARNO, respectively. Error bars indicate values of $1/t_{1/2}$ observed in two independent experiments.

ARF1 does not fit to a single exponential function. This is probably linked to the fact that the reaction does not occur in solution but at the membrane surface. For each fluorescence recording, the apparent half-time ($t_{1/2}$) of ARF deactivation was determined graphically. Variation in the value of $1/t_{1/2}$ was <5% when determined from duplicate experiments using the same batch of vesicles and <30% when different lipid vesicle preparations were used.

RESULTS AND DISCUSSION

To examine whether ARF1 GAP interacts specifically with certain lipids, we analyzed the activity of a truncated but fully active form of ARF1 GAP, $1-257$ GAP, on ARF1_{GTP} bound to unilamellar lipid vesicles of controlled composition, always including 30% PS. The decrease of ARF1 tryptophan fluorescence that occurs upon GTP hydrolysis was used to monitor the reaction in real time. With vesicles containing 70% egg PC, the deactivation of ARF1 upon the addition of a catalytic amount of ARF1 GAP occurred very slowly (Fig. 1A). The kinetics was not accelerated by incorporating 10% PA or 5% PIP₂ at the expense of PC. By contrast, a 10-fold increase in the rate of GAP-catalyzed hydrolysis of GTP on ARF1 was observed upon the incorporation of 10% 1,2-dioleoylglycerol (1,2-DOG), a diacylglycerol with two monounsaturated acyl chains (C18:1). An opposite pattern emerged when the same lipids were tested for their effects on the exchange activity of ARNO (Fig. 1B). With 1,2-DOG- or PA-containing vesicles, ARNO-catalyzed activation of ARF1 was as slow as with control vesicles, but in the presence of 5% PIP₂ it was dramatically increased, in agreement with our previous study demonstrating the binding of

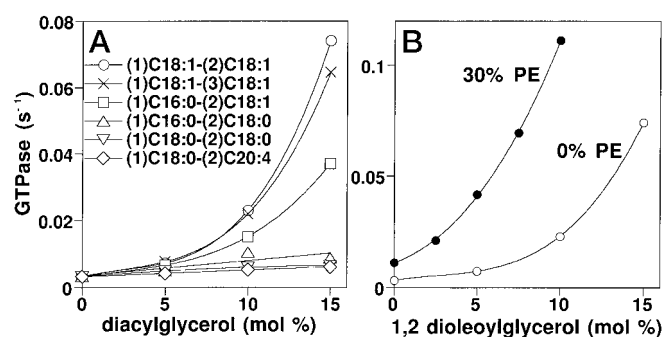


FIG. 2. Dose-response curves for the effect of different DAGs on $1-257$ GAP activity. The activity of $1-257$ GAP was measured as in Fig. 1A with increasing molar proportion of the indicated DAG at the expense of egg PC in lipid vesicles. *A*, dose-response curves for different DAG isomers in vesicles containing 30% brain PS and egg PC as the remaining lipid. *B*, dose-response curves for 1,2-DOG in vesicles containing 30% brain PS, 0 (○) or 30% egg PE (●); egg PC was the remaining lipid.

ARNO to PIP₂-containing vesicles through its PH domain (9). Thus, the two reactions of the activation/deactivation cycle of ARF1 are differentially regulated by lipids: PIP₂ accelerates ARNO-catalyzed GDP/GTP exchange, whereas 1,2-DOG accelerates GAP-catalyzed hydrolysis of GTP on ARF1.

Several diacylglycerols (DAGs) were compared for their ability to activate ARF1 GAP (Fig. 2A). Three striking observations were made. First, 1,3-DOG was as active as 1,2-DOG. Therefore, a specific recognition by ARF1 GAP of the esterified positions of the glycerol backbone, like that found for the interaction of protein kinase C with DAG (13), can be ruled out. It is noteworthy that TPA, a phorbol ester that mimics the glycerol part of DAG and activates protein kinase C, did not activate ARF1 GAP (data not shown). Second, the DAG dose responses were nonlinear. This also rules out a simple 1:1 lipid-protein interaction. Third, activation of ARF1 GAP by DAG was highly dependent on the nature of the acyl chains, another difference from protein kinase C for which large changes in the composition of the acyl chains are tolerated (13). DAGs with two saturated acyl chains had only marginal effects on ARF1 GAP activity. Only DAGs with one or two monounsaturated acyl chains (oleoyl) were potent activators of ARF1 GAP. Surprisingly, 1-stearoyl-2-arachidonoyl-glycerol, a DAG containing one saturated acyl chain and one polyunsaturated acyl chain, was inactive. It is noteworthy that monounsaturated and polyunsaturated DAGs are generated by different phospholipid signaling pathways. Monounsaturated DAGs derive mainly from the hydrolysis of PC into DAG by the sequential action of PLD and phosphatidate phosphatase, whereas polyunsaturated DAGs derive almost exclusively from the hydrolysis of PIP₂ by PI-phospholipase C (14, 15). Therefore, the activation of ARF1 GAP by DAGs with monounsaturated acyl chains suggests that ARF1 GAP activity is controlled by the PLD pathway.

In the Golgi, the level of DAG is mainly in balance with that of PC. Indeed, not only the PLD pathway but also the sphingomyelin pathway generate DAGs at the expense of PC, whereas the CDP-choline pathway consumes DAG in favor of PC synthesis (16, 17). Interestingly, 1,2-DOG and PC have opposing effects on ARF1 GAP activity. PC seems inhibitory when compared with the other major neutral phospholipid component of membranes, PE, which differs from PC only by having a smaller and less hydrated polar head. When the proportion of PC was reduced in favor of PE, the basal ARF1 GAP activity in the absence of DAG was increased, and the 1,2-DOG dose response curve was shifted to lower surface concentrations (Figs. 2B and 3A). Similar enhancements were

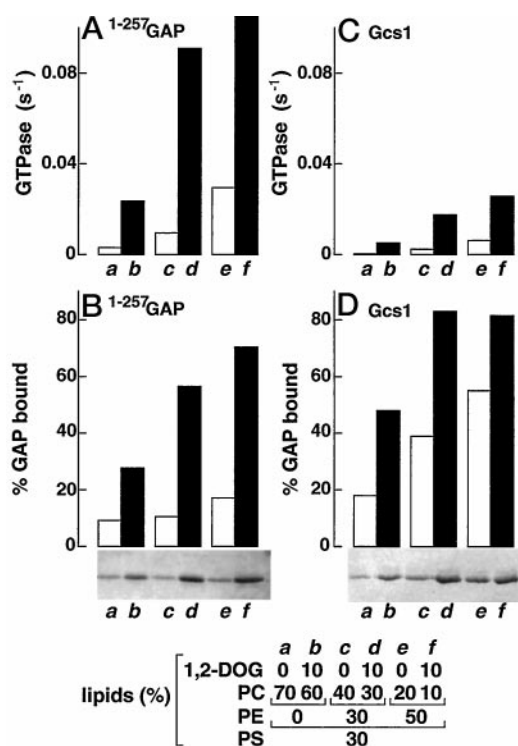


FIG. 3. Opposing effects of 1,2-DOG and PC on the activity (A and C) and the membrane binding (B and D) of $^{1-257}$ GAP (A and B) and the yeast Gcs1 protein (C and D). The activity of $^{1-257}$ GAP or Gcs1 on ARF1_{GTP} bound to unilamellar vesicles containing the indicated mol % of brain PS, egg PC, egg PE, and 1,2-DOG was measured as in Fig. 1A. The binding of $^{1-257}$ GAP and Gcs1 to vesicles was measured by a sedimentation assay (see “Experimental Procedures”). $^{1-257}$ GAP and Gcs1 in the pellet were visualized by Coomassie Blue staining after SDS-polyacrylamide gel electrophoresis. Data shown are representative of at least two independent experiments.

observed when other phospholipids (PS, phosphatidylglycerol, or PA) were incorporated at the expense of PC (data not shown), suggesting that ARF1 GAP activity is inhibited by PC rather than activated by a specific phospholipid. By combining the opposite effects of 1,2-DOG and PC, the activity of ARF1 GAP may be varied *in vitro* by 2 orders of magnitude. This high sensitivity to membrane composition implies that any lipid pathway that modifies the relative amounts of PC and 1,2-DOG at the cytoplasmic surface of Golgi vesicles will have a dramatic effect on ARF1 GAP activity.

To determine whether 1,2-DOG acts directly on ARF1 GAP, we studied the binding of $^{1-257}$ GAP to ARF-free lipid vesicles by sedimentation. The presence of 10% 1,2-DOG and the substitution of PE for PC enhanced the binding of $^{1-257}$ GAP to vesicles (Fig. 3B), whereas the presence of 1-stearoyl-2-arachidonoyl-glycerol did not (data not shown). Thus, a good correlation was observed between $^{1-257}$ GAP activity on membrane-bound ARF1_{GTP} (Fig. 3A) and $^{1-257}$ GAP translocation to vesicles (Fig. 3B). By contrast, the near total partitioning of ARF1_{GTP} with the membrane was not affected by these changes in the lipid composition (data not shown). Thus, 1,2-DOG stimulates the activity of ARF1 GAP by promoting its membrane recruitment, hence favoring its interaction with membrane-bound ARF1_{GTP}, whereas PC inhibits ARF1 GAP activity by hindering its translocation to vesicles.

Similar experiments were performed with Gcs1, a yeast homolog of ARF1 GAP that can be produced as a full-length protein in *E. coli* (10). Gcs1 was one-fourth as active on bovine ARF1_{GTP} as $^{1-257}$ GAP, but it was similarly affected by 1,2-DOG and PC for its activity (Fig. 3C) and for its binding to vesicles (Fig. 3D). Gcs1 and ARF1 GAP show a high degree of similarity

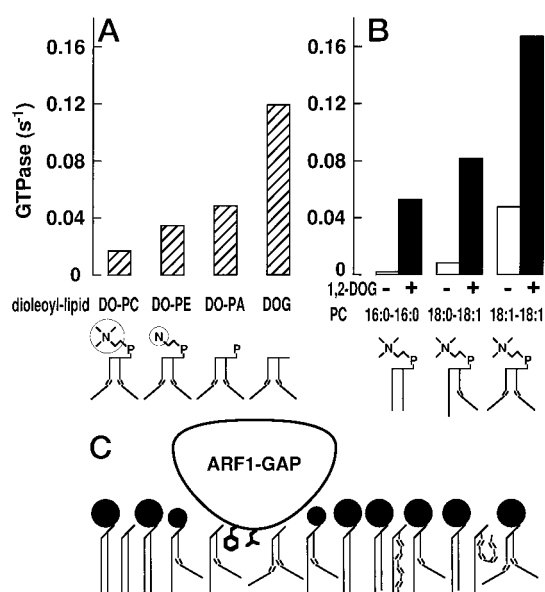


FIG. 4. Effects of the size of the lipid polar head and of the nature of the lipid acyl chains on ARF1 GAP activity. The various lipids tested are represented schematically to emphasize the relative size of their polar head groups and hydrocarbon chains. A, ARF1 GAP activity with vesicles containing 30% brain PS, 30% egg PC, 30% egg PE, and 10% of the indicated 1,2-dioleoyl-lipid. B, ARF1 GAP activity with vesicles containing 30% brain PS; 30% egg PE; 0% (white bars) or 10% (black bars) 1,2-DOG; and the indicated synthetic PC as the remaining lipid. $^{1-257}$ GAP activity on ARF1_{GTP} was measured as in Fig. 1A. Data shown are representative of at least two independent experiments. C, model for the interaction of ARF1 GAP with lipid vesicles. Thanks to their lack of a polar head and their bent acyl chains, DAGs with one or two monounsaturated acyl chains may facilitate the insertion of some hydrophobic amino acids of ARF1 GAP.

in their first 100 amino acids, which include a zinc finger motif (4, 11). This sequence, which is also shared by other proteins, such as centaurins (the function of which is unknown (18–20)), could define a protein motif involved in catalysis of the GTP hydrolysis of the members of the ARF family and/or binding to membrane regions containing monounsaturated DAGs originating from the hydrolysis of PC. However, this does not preclude additional or different mechanisms for regulation by lipids. Partially purified ARF1 GAP proteins, distinct from the protein studied here, have been shown to be activated by phosphoinositides (21, 22).

To further analyze the mechanisms by which PC hinders and 1,2-DOG promotes the binding of ARF1 GAP or Gcs1 to lipid vesicles, we systematically varied the vesicle composition, using synthetic lipids of strictly defined acyl chains. A simple rule emerged: the activity of ARF1 GAP is a function of the relative volumes occupied by the polar head and the hydrocarbon chains of the lipids. ARF1 GAP activity increased when the size of the polar head decreased (PC < PE < PA < DAG; Fig. 4A) and when the number of monounsaturated acyl chains in DAG (Fig. 2A) or even in PC (Fig. 4B) increased (C16:0-C16:0 < C16:0-C18:1 < C18:1-C18:1). Thus, the inhibition of ARF1 GAP by PC and its activation by 1,2-DOG have the same physical basis: 1,2-DOG is a cone-shaped lipid. It lacks a polar head and occupies a large hydrophobic volume because the *cis* double bond induces a bend at the middle of the hydrocarbon chain. By contrast, saturated PCs have a large hydrated polar head, and their acyl chains occupy a cylindrical hydrophobic volume of small section. Other lipids display intermediate shapes between these two extreme cases. We speculate that rather than involving a specific lipid recognition, the binding of ARF-GAP1 to membranes is mainly driven by hydrophobic contact of the protein with the lipid hydrocarbon chains near their interface

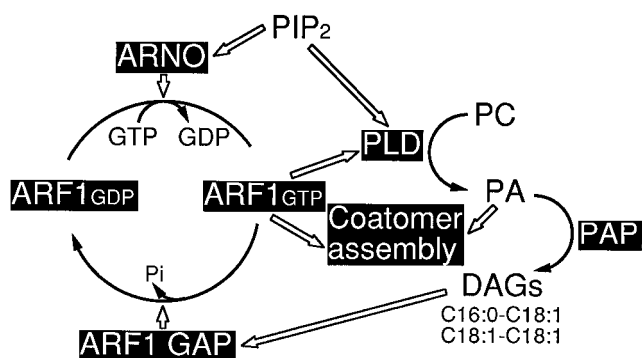


FIG. 5. Model for the effect of lipids on the GTP cycle of ARF1. ARF1 is activated by the PIP₂-sensitive guanine nucleotide exchange factor ARNO (9). Membrane-bound ARF1_{GTP} activates PLD, which is also PIP₂-sensitive and hydrolyses PC into PA (5, 6, 8). Both PA and ARF1_{GTP} may contribute to the recruitment of coat proteins that lead to vesicle budding (7, 27). DAGs with monounsaturated acyl chains are generated from PA upon the action of PA phosphohydrolase. These DAGs promote the recruitment of ARF1 GAP, which catalyzes GTP hydrolysis on ARF1. ARF1_{GDP} recycles in the cytosol, and the coatomer dissociates.

with the glycerol backbone (Fig. 4C). Such a relatively deep penetration is probably hindered by large lipid polar head groups and favored by monounsaturated acyl chains. By spreading apart, these bent acyl chains leave intermolecular "cavities," in which hydrophobic amino acids of ARF1 GAP could insert. The striking observation that 1-stearoyl-2-arachidonoyl-glycerol behaves like a saturated DAG rather than a DAG with a monounsaturated oleoyl chain was also demonstrated with the corresponding fatty acids: addition to the vesicles of 10% oleate significantly increased ARF1 GAP activity, whereas the same amount of arachidonate or palmitate did not (data not shown). This agrees with model studies suggesting that the conformation of the arachidonoyl chain in the lipid layer is closer to that of a rigid saturated alkyl chain than to that of a bent oleoyl chain (23). Alternatively, the arachidonoyl chain could adopt a hairpin shape. Such a conformation could also be unfavorable for the penetration of hydrophobic residues because it does not create a cavity below the glycerol backbone but rather a steric hindrance.

Our finding that PC-derived DAGs activate ARF1 GAP by promoting its translocation to the vesicle has several implications. First, it suggests a function for PC-derived DAGs, which *in vivo* do not activate most protein kinase C isozymes because the PLD pathway, in contrast to the phospholipase C pathway, is not accompanied by an increase in intracellular calcium (24, 25). A recent study on yeast strains with secretion defects highlights the role of DAG in Golgi vesicular transport (26). The Sec14 protein negatively regulates the CDP-choline pathway, which consumes DAG to produce PC. Sec14p is essential for vesicular transport, but this requirement is bypassed upon blocking the CDP-choline pathway or overproducing DAG by another lipid pathway. Thus, preservation of a DAG pool at the

expense of PC seems essential for Golgi function in yeast. ARF1 GAP could be one of the putative DAG "sensors." Finally, the activation of ARF1 GAP by PC-derived DAG suggests a feedback loop linking the translocation of ARF1 GAP to vesicles with the activation of PLD by ARF1_{GTP} (Fig. 5). The production of PA from PC hydrolysis by ARF1-activated PLD contributes to the binding of the coatomer to vesicles (7). After a sustained activation of PLD by ARF1_{GTP}, DAGs may accumulate and trigger ARF1 GAP translocation to vesicles, leading to GTP hydrolysis on ARF1 and coatomer disassembly. This would ensure a fine control of the duration of vesicle coating.

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