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RESEARCH ARTICLE

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Hypothesis: Chemical activity regulates and coordinates the processes maintaining glycerophospholipid homeostasis in mammalian cells

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Abstract

Mammalian cells maintain the complex glycerophospholipid (GPL) class compositions of their various membranes within close limits because this is essential to their well-being or viability. Surprisingly, however, it is still not understood how those compositions are maintained except that GPL synthesis and degradation are closely coordinated. Here, we hypothesize that abrupt changes in the chemical activity of the individual GPL classes coordinate synthesis and degradation as well other the homeostatic processes. We have previously proposed that only a limited number of "allowed" or "optimal" GPL class compositions exist in cellular membranes because those compositions are energetically more favorable than others, that is, they represent local free energy minima (Somerharju et al 2009, Biochim. Biophys. Acta 1788, 12-23). This model, however, could not satisfactorily explain how the "optimal" compositions are sensed by the key homeostatic enzymes, that is, rate-limiting synthetizing enzymes and homeostatic phospholipases. We now hypothesize that when the mole fraction of a GPL class exceeds an optimal value, its chemical activity abruptly increases which (a) increases its propensity to efflux from the membrane thus making it susceptible for hydrolysis by homeostatic phospholipases; (b) increases its potency to inhibit its own biosynthesis via a feedback mechanism; (c) enhances its conversion to another glycerophospholipid class via a novel process termed "head group remodeling" or (d) enhances its translocation to other subcellular membranes. In summary, abrupt change in the chemical activity of the individual GPL classes is proposed to regulate and coordinate those four processes maintaining GPL class homeostasis in mammalian cells.

KEYWORDS

coordination, homeostasis, maintenance, metabolism, set point

Abbreviations: CCT, CTP:phosphocholine cytidylyltransferase; CL, cardiolipin; DAG, diacylglycerol; GPL, glycerophospholipid; PA, phosphatidic acid; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PG, phosphatidylglycerol; PI, phosphatidylinositol; PLA, phospholipase A; PLC, phospholipase C; PS, phosphatidylserine; SL, superlattice; TAG, triacylglycerol.

1 | INTRODUCTION

Glycerophospholipids (GPLs) form the backbone of all membranes in mammalian cells. The major GPL classes are phosphatidylcholine (PC), -ethanolamine (PE), -inositol (PI), -serine (PS), -glycerol (PG), phosphatidic acid (PA) and cardiolipin (CL) and the relative concentrations (mole fractions) of these GPLs are kept within close limits in mammalian cells and tissues[1] apparently because deviations from the "optimal" composition can have dire consequences.[2-6] Remarkably, however, despite the vital importance of GPL homeostasis, the mechanisms underlying this crucial phenomenon is poorly understood, except for that biosynthesis and degradation are tightly coordinated. Such coordination is demonstrated, for example, by that when the synthesis of PC was increased several-fold, its concentration remained essentially unchanged due to increased degradation.[7-11] Parallel evidence has been obtained for PE and PS.[7,9,11,12] Conversely, when the synthesis of PC, PE or PS was inhibited, their turnover decreased correspondingly.[13-17] However, there it is no information on how the synthesis and degradation are coordinated, which must be a challenging task due to the presence of many GPL classes in the same membrane (Figure 1). The key challenge derives from the fact that when the mole fraction (relative concentration) of a single GPL class changes, the mole fractions of all other GPL classes are simultaneously altered. Accordingly, the mechanisms controlling the mole fractions of the individual GPL classes must be acutely and accurately coordinated to maintain homeostasis. As far as we are aware, no model or theory on how the coordination is accomplished has been put forward.

Here, we present a hypothesis proposing that the abrupt, composition-dependent changes in the chemical activity of the individual GPL classes regulate and coordinate their synthesis and degradation thus maintaining GPL homeostasis in mammalian cells. This hypothesis, inspired by our recent findings on the processes involved in GPL homeostasis, represents a major extension of the previously proposed Superlattice model.

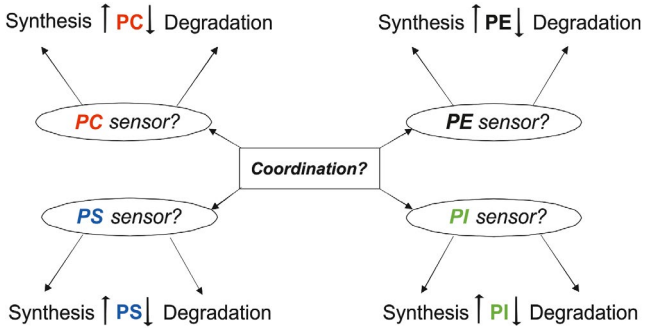

FIGURE 1 Complexity of regulation of the glycerophospholipid (GPL) compositions of mammalian membranes. This scheme emphasizes the complexity of regulation of the GPL compositions of membranes consisting of many different lipid classes. All GPL classes present in mammalian cells are not shown here for simplicity

1.1 | Superlattice model and its shortcomings

We have previously shown that the GPL compositions of the inner and outer leaflets of mammalian erythrocyte and platelet membranes are remarkably similar to compositions predicted by the so-called Superlattice (SL) Model, which proposes that there is a limited number of "allowed" GPL mole fractions.[18,19] Accordingly, the relative concentrations of the different phospholipid classes tend to settle in "allowed" values because that provides the optimal interaction between the proximal molecules, that is, a free energy minimum. The model could not, however, adequately explain how the "allowed" compositions are maintained in the membranes of nucleated cells in which the GPLs are continuously synthetized and degraded.

Regarding synthesis, the SL-model proposed that when the mole fraction of a particular GPL reaches a value allowed by the model, membrane lateral order increases abruptly which leads to aggregation of the respective synthetizing enzyme thus inactivating it.[19] Correspondingly, when the mole fraction of the particular GPL class falls below its critical value, the superlattice would collapse and, consequently, membrane order would drop abruptly thus reactivating of the enzyme synthetizing the particular GPL. As far as we are aware, such regulatory mechanism is not supported by the data published thus far and seems thus unlikely.

Regarding degradation, the SL-model proposed that when the mole fraction of a particular GPL exceeds a critical value, segregated lateral domains would appear and then homeostatic phospholipases, activated by poorly packed domain boundaries, would hydrolyze the GPL molecules in excess. Once the GPL in excess had been degraded, the segregated domains and the boundaries would disappear thus rendering the phospholipases inactive. A serious shortcoming of this model is that it could not explain why only the molecules in excess would be degraded by homeostatic phospholipases? In conclusion, it remained speculative how the synthesis and degradation of GPLs are regulated and coordinated so that homeostasis is maintained in growing cells in which GPLs are continuously synthetized and degraded.

Due to the shortcomings indicated above as well as recent novel data of the synthesis and degradation of GPLs[20-23] we hypothesize here that the *chemical activity* of the different GPLs regulate and coordinate their metabolism thus maintaining the GPL homeostasis. We propose (a) that when the mole fraction of one GPL class deviates from an optimal value, its chemical activity changes abruptly due to weakened interactions with the proximal molecules (Figure 2) and (b) such abrupt changes in the chemical activity of the different GPLs regulate and

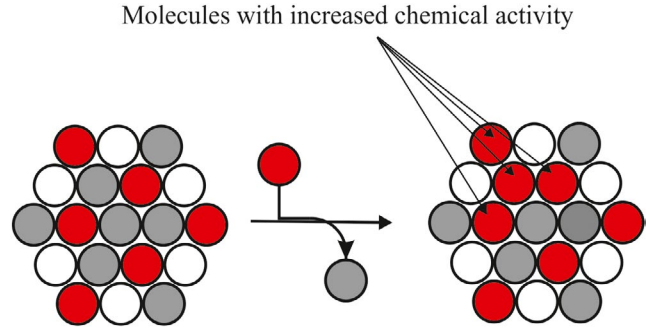

FIGURE 2 Deviation from an optimal composition brings about several glycerophospholipid (GPL) molecules with an increased chemical activity. On the left: The GPL class composition is optimal as proposed previously for the erythrocyte membrane inner leaflet where PE (gray) is ~44 mol%, the choline lipids (white) are ~22 mol% and the negatively charged GPLs (red) are ~33 mol%.[18] Note that at this composition there are no proximal (strongly repelling) negatively charged GPLs. On the right: If a (zwitterionic) GPL molecule is replaced by a negatively charged one, the chemical activity of three or four negatively charged GPL molecules is greatly increased due to electrostatic repulsion between the proximal negatively charged GPLs. If the mole fraction of an zwitterionic GPL increases above its optimal value (not shown here), its chemical activity is predicted to increase due to weakened van der Waals or hydrogen bonding interactions with its neighbors, or steric strain

coordinate multiple homeostatic process including synthesis, degradation, interconversion (head group remodeling), and interorganelle translocation of GPLs (Figure 3). Below we will discuss in more detail the evidence suggesting that chemical activity could indeed regulate each of these processes.

1.2 | Chemical activity regulates GPL biosynthesis

Excluding PS and PC, it is poorly established what regulates the biosynthesis of GPLs in mammalian cells. Kuge and coworkers have demonstrated that PS strongly inhibits its own synthesis in CHO cells and that this inhibition is most probably mediated by the interaction of PS with a specific arginine in PS synthase 1 or 2 (reviewed in ref. [[24]]). In the synthesis of PC the rate limiting, and thus the regulatory step, is the binding of CTP:phosphocholine cytidylyltransferase (CCT) to the ER or nuclear membrane.[25] The binding is inhibited by lyso-PC and stimulated by PE, diacylglycerol (DAG) and negatively charged lipids, and it has been proposed that the ratio of those lipids differently modulate the membrane packing (or curvature elastic stress) or charge of the ER membrane thus regulating CCT binding to the membrane.[26,27] Early studies have also indicated that, beside PS and PC, the synthesis of PI may also be regulated by a feed-back mechanism in rat pituitary cells,[28] but the details of this process remain unclear. Recently, we have shown that loading of any common GPL to HeLa, BHK-21, or CHO cells strongly inhibited the synthesis of the corresponding GPL class.[22,23] The GPL molecules in excess in a membrane should have an increased chemical activity, which should promote their binding to the active or a regulatory site of the synthetizing enzyme thus inhibiting its activity. Alternatively, the molecules in excess could, for example, in case of CTT, inhibit membrane association and thus the activity of the synthetizing enzyme. In conclusion, chemical activity of GPLs is proposed to be the factor regulating the rate-limiting enzymes of

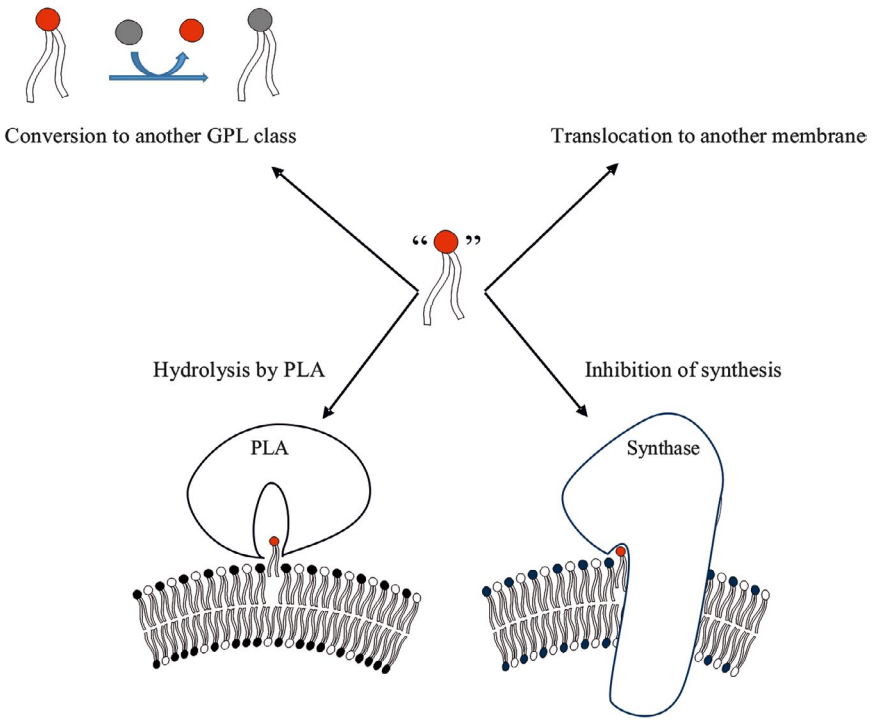

FIGURE 3 Multiple homeostatic events can be driven by increased chemical activity of the glycerophospholipids (GPLs) present in excess. As discussed in the text, the GPL molecules present in excess (red) has increased chemical activity which is predicted to (a) increase its hydrolysis by a phospholipase A; (b) inhibit its own biosynthesis; (c) enhance its conversion to another GPL with a different head group (=head group remodeling), or (d) enhance its translocation to another membrane. All these events are may occur simultaneously to maintain GPL class homeostasis in mammalian cells

biosynthesis via a feed-back mechanism. Previously, chemical activity of cholesterol has been suggested to regulate its biosynthesis.[29,30]

1.3 | Increased chemical activity renders GPLS susceptible to hydrolysis by homeostatic phospholipases

There is good evidence that Ca^{2+}-independent PLAs (iPLAs alias PNPLAs) are the key players in homeostatic degradation of GPLs in mammalian cells[9,10,31-33] as discussed in more detail elsewhere.[1] Consistently, we have recently shown that PNPLA9, −6, and −4 catalyze homeostatic degradation of PC, PE, and PS in human cells.[21] More importantly, we have provided strong evidence that the activity of PNPLA9 in vitro is proportional to the propensity of its GPL substrate to efflux from the membrane[20] to the active site of PNPLA9, predicted to reside well above the membrane surface.[34] Since the efflux propensity of a GPL molecule should be proportional to its chemical activity, we propose that the rate of homeostatic degradation of GPLs correlates positively on their chemical activity.

1.4 | Chemical activity drives GPL glass interconversion (head group remodeling)

We have recently found that exogenous PE, PS, PI, PG, and PA are rapidly and effectively converted to PC when loaded to HeLa cells.[22,23] Notably, blocking of fatty acyl-CoA formation with Triacsin C had no effect on the conversion to PC thus excluding the possibility that deacylation of the GPL precursor, followed by incorporation of released fatty acids to PC *via* synthesis de novo is involved in the process. Extensive knock-down studies indicated that different enzymes (including PLCs or similar enzymes) catalyze the initial, committed step of the interconversion or "head group remodeling".[23] Since loading of an exogenous GPL to the cells should greatly increase the chemical activity of the respective GPL class, it is most likely that chemical activity drives head group remodeling. A particular benefit of this novel homeostatic process is that it requires far less cellular energy than biosynthesis de novo, simply because the fatty acids need not to be activated to CoA derivatives.

1.5 | Interorganelle translocation of GPLs, yet another process affected by chemical activity

As suggested earlier, when the molar fraction of a GPL class increases above an optimal value, its chemical activity and thus its propensity to efflux from a membrane should increase abruptly. It has been previously shown that the rate-limiting step in spontaneous intermembrane translocation of a lipid is its efflux from the donor membrane.[35,36] While spontaneous intermembrane translocation of lipids is often considered negligible, this does not apply to all lipids as their hydrophobicity varies by orders of magnitude.[37] Notably, efflux from the donor membrane seems to be the rate-limiting step in protein-mediated translocation processes as well.[38,39] It is also worthy to note that interorganelle translocation of a GPL is necessarily coupled to its biosynthesis,[40] since the translocation affects the concentration of that GPL both in the donor and acceptors membranes and thus the efficiency of feedback inhibition of biosynthesis in either membrane. In conclusion, if the mole fraction of a GPL in a membrane increases, its chemical activity and, consequently, its intracellular translocation is also likely to increase as has been previously proposed for cholesterol.[29,41,42]

1.6 | Other modes of regulation

Finally, we stress that beside the ones proposed here there are also other mechanisms that regulate GPL composition of mammalian cells, such as those depending on altered gene expression or translation. However, those mechanisms are far too slow to acutely regulate the GPL composition without energy wasting fluctuations (hysteresis). Those "coarse" mechanisms rather come into play when a change in GPL composition is required as, for example, during mitosis, cell differentiation or by altered cellular environment.[8,43-45] In principle, protein phosphorylation (or other modifications) could play a role in acute regulation of GPL compositions since those processes can take place rapidly and can influence protein activity.[46-49] However, this mechanism requires the existence of proteins that accurately "sense" the change in the GPL class composition of the membrane. As far as we are aware, no such proteins have been identified in mammalian cells so far. Notably, even if such sensor proteins do exist, they as well are likely to respond to variations in the chemical activity of the different GPL classes. In conclusion, abrupt variations in the chemical activity of the individual GPL classes are most probably the primary factor regulating GPL homeostasis.

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CONFLICT OF INTEREST

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

P. Somerharju, J. Virtanen, and M. Hermansson wrote the paper.

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