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Lipid topogenesis — 35 years on

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ABSTRACT

Glycerophospholipids are the principal fabric of cellular membranes. The pathways by which these lipids are synthesized were elucidated mainly through the work of Kennedy and colleagues in the late 1950s and early 1960s. Subsequently, attention turned to cell biological aspects of lipids: Where in the cell are lipids synthesized? How are lipids integrated into membranes to form a bilayer? How are they sorted and transported from their site of synthesis to other cellular destinations? These topics, collectively termed 'lipid topogenesis', were the subject of a review article in 1981 by Bell, Ballas and Coleman. We now assess what has been learned about early events of lipid topogenesis, i.e. "lipid synthesis, the integration of lipids into membranes, and lipid translocation across membranes", in the 35 years since the publication of this important review. We highlight the recent elucidation of the X-ray structures of key membrane enzymes of glycerophospholipid synthesis, progress on identifying lipid scramblase proteins needed to equilibrate lipids across membranes, and new complexities in the subcellular location and membrane topology of phosphatidylinositol synthesis revealed through a comparison of two unicellular model eukaryotes.

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1. Introduction

Thirty-five years ago, Bell, Ballas and Coleman published a review article entitled 'Lipid topogenesis' [1]. The previous year, Blobel had published an article entitled 'Intracellular protein topogenesis' [2] (see also the related review by Rothman and Lenard [3]). Both articles focused on the endoplasmic reticulum (ER), a biogenic membrane capable of synthesizing and integrating its lipid and protein components. The term topogenesis is not found in the Oxford English Dictionary but was used in both papers to describe events that accompany and follow the synthesis of membrane components. Early topogenic events comprise those that occur concurrently with – or soon after – the synthesis of lipids and proteins, whereas late events refer to the processes whereby these molecules are sorted and exported from the ER to reach other cellular destinations. These are fundamental processes that describe the biogenesis of cellular membranes.

Cells synthesize a diverse array of glycerophospholipids and other lipids. The question of why there are so many lipid species has been discussed [4–6]. Thus, lipid diversity is necessary to generate thin and thick cell membranes with biogenic and barrier functions, provide transbilayer charge asymmetry, endow membranes with adaptive properties that allow them to tolerate changes in temperature by eliminating phase transitions, enable membranes to curve, bend and be sculpted into vesicles, provide a wide range of signaling molecules, and support the activities of membrane proteins many of which require a particular lipid environment and specific lipid cofactors. The diverse spectrum of cellular lipids is synthesized via complex, sometimes parallel and often essential pathways, and lipid diversity is increased and homeostatically maintained by remodeling reactions in which acyl chains are removed and replaced. The paradigmatic pathways of glycerophospholipid biosynthesis were elucidated in the late 1950s and early 1960s [7,8] and highlight the central role of cytidine nucleotides. These pathways, termed the Kennedy pathways, are shown in Fig. 1. Biosynthesis requires CDP-alcohol phosphotransferase enzymes that catalyze the formation of a phosphodiester bond linking the head and tail components of the lipid. For this, the head or tail of the lipid enters the enzymatic reaction as an activated (high energy) precursor in the form of a CDP-alcohol. Transfer to a cognate acceptor alcohol (a tail or a head, respectively) results in the formation of a phospholipid. Thus, a water-soluble CDP-alcohol (headgroup donor) may be combined with diacylglycerol (DAG) as in the case of phosphatidylcholine (PC) synthesis. Alternatively, a lipophilic CDP-alcohol, CDP-DAG, may

Abbreviations: C/EPT, choline/ethanolamine phosphotransferase; CDP, cytidine diphosphate; CDS, CDP-DAG synthase; CL, cardiolipin; DGAT, diacylglycerol acyltransferase; DIPPS, di-*myo*-inositol-1,3′-phosphate-1′-phosphate synthase; GPCR, G protein-coupled receptor; GPI, glycosylphosphatidylinositol; IPCT, L-myo-inositol-1-phosphate cytidylyltransferase; PA, phosphatidic acid; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PG, phosphatidylglycerol; PI, phosphatidylinositol; PIPS, phosphatidylinositol-phosphate synthase; PIS, phosphatidylinositol synthase.

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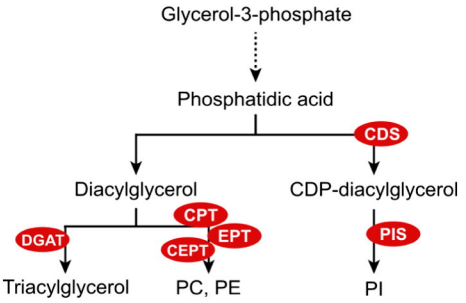

Fig. 1. *The Kennedy pathways of glycerophospholipid synthesis.* Phosphatidic acid is synthesized in multiple steps from glycerol-3-phosphate (obtained from glycolysis or the phosphorylation of glycerol) and fatty acyl-CoA. It is the precursor of diacylglycerol and the liponucleotide CDP-diacylglycerol, both of which are used for phospholipid biosynthesis. Phospholipids are synthesized by pathways that use a CDP-alcohol as an activated precursor. The activated lipid tail CDP-diacylglycerol is used, for example, in the synthesis of phosphatidylinositol (PI) in eukaryotes and PS and PI-phosphates in prokaryotes. Alternatively, a water-soluble CDP-alcohol, e.g. CDP-choline or CDP-ethanolamine, is combined with diacylglycerol to generate phosphatidylcholine (PC) or phosphatidylethanolamine (PE). Diacylglycerol is also used for the synthesis of the neutral lipid triacylglycerol. CDS, cytidine-diphosphate diacylglycerol synthase; CPT, cholinephosphotransferase; CEPT, choline/ethanolamine phosphotransferase; DGAT, diacylglycerol acyltransferase; EPT, ethanolamine phosphotransferase; PIS, phosphatidylinositol synthase.

be used in conjunction with a non-activated headgroup as in the case of phosphatidylinositol (PI) synthesis. The reaction can be written generically as:

$$\text{CDP-}R_1 + R_2 \rightarrow R_1\text{-}\mathbf{P}\text{-}R_2 + \text{CMP}$$

(where R_1 and R_2 correspond to the head and tail components of the phospholipid (R_1-**P**-R_2), or vice versa, and **P** indicates a phosphodiester bond).

The main conclusion of the Bell et al. review [1] was that CDP-alcohol phosphotransferase-catalyzed lipid biosynthetic reactions are carried out on the cytoplasmic face of the ER by membrane-bound enzymes. Thus lipid synthesis is asymmetric, resulting in the deposition of new phospholipids into the cytoplasmic leaflet of the ER membrane. There is no parallel biosynthetic pathway to generate phospholipids in the luminal leaflet of the ER. Thus, propagation of the lipid bilayer requires newly synthesized lipids to be translocated across the membrane to populate the luminal leaflet. As spontaneous transbilayer translocation of phospholipids does not occur at an appreciable rate, it was assumed that a lipid transporter – a scramblase protein – must be involved. Much of the experimental work supporting these conclusions was obtained via studies on sealed rat liver microsomes. Bell et al. discussed experiments where proteases and membrane impermeant inhibitors were used to probe the orientation of the active sites of lipid biosynthetic enzymes in microsomes, and in which the transport (or lack thereof) of substrates such as CDP-choline and palmitoyl-CoA into the vesicles was measured and localization of lipid products was determined by phospholipases or chemical modification.

Despite the concurrency of the two review articles on protein and lipid topogenesis, studies of protein topogenesis have yielded a wealth of information [9,10] whereas progress on lipid aspects has been comparatively slow. However, with relatively recent advances in certain areas such as lipidomics [5,11,12] and live cell imaging of lipids [13, 109], the understanding of late lipid topogenic events has steadily improved. In contrast, early topogenic events remain poorly defined but the prospects for improvement here are bright. For example, in the past couple of years there has been an explosion of structural information on lipid biosynthetic enzymes [14–17] and while as yet there is no indication of the molecular identity of the scramblase that is needed to redistribute newly synthesized lipids between the two leaflets of the ER membrane [18], the recent discovery of other scramblase proteins [19–24] lends hope that the identity of the ER scramblase will soon be revealed. Here our objective is to review these recent advances and to assess what has been learned about early events of lipid topogenesis, i.e. 'lipid synthesis, the integration of lipids into membranes, and lipid translocation across membranes' [1], in the 35 years since the publication of the review by Bell and colleagues.

2. CDP-alcohol phosphatidyltransferase enzymes

The Bell et al. review [1] is best known for capturing the concept that glycerophospholipids are synthesized on the cytoplasmic face of the ER, and that newly synthesized phospholipids must redistribute across the membrane in order to expand the bilayer uniformly. This conclusion is depicted pictorially in Fig. 2, which also shows the best current assessment of the membrane topology of CEPT, the choline/ethanolamine phosphotransferase enzyme that generates phosphatidylcholine (PC) and phosphatidylethanolamine (PE) in the ER membrane from the corresponding CDP-alcohol and diacylglycerol (DAG). Active site residues of CEPT are found within a cytoplasmic loop between the first and second transmembrane domain. The choline-specific CPT enzyme is located in the Golgi apparatus, but has a similar predicted membrane topology [25]. PA provides DAG in the ER, whereas Golgi DAG may be a byproduct of sphingomyelin synthesis.

CEPT, CPT and EPT (Fig. 1) are members of the CDP-alcohol phosphotransferase family. These enzymes catalyze the scission of a phosphoanhydride bond to release CMP from a CDP-alcohol, with the concomitant formation of a phosphodiester bond (Fig. 2). Beyond scanning mutagenesis studies supplemented with bioinformatics to define active site residues, and the use of membrane topology prediction algorithms to determine the orientation of the active site with respect to the membrane (Fig. 2) [25], no molecular information was available on this class of enzymes. However, the recent reports of the X-ray structures of two CDP-alcohol phosphotransferases [15,16] from the hyperthermophilic archaeon *Archaeoglobus fulgidus* that use a

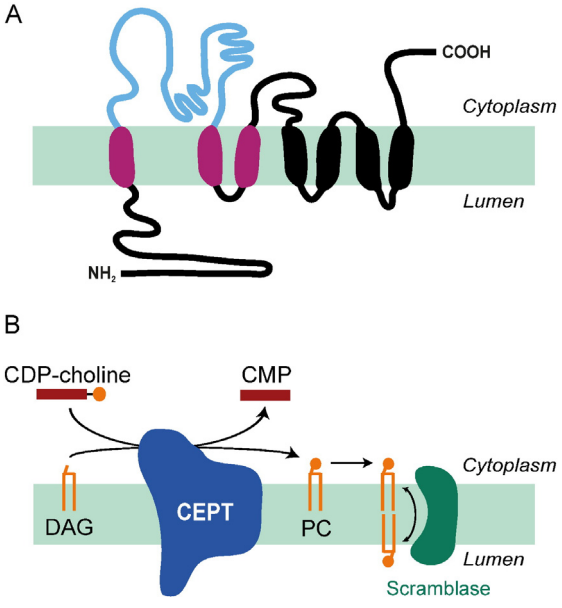

Fig. 2. *Asymmetric synthesis and transbilayer scrambling of phosphatidylcholine in the ER. A*, Predicted membrane topology of human CEPT1 [25]. Regions of CEPT necessary for binding diacylglycerol (DAG) are shown in pink, and the amino acid stretch needed for CDP-alcohol binding and enzymatic activity is shown in light blue [25]. The light blue region also contains the consensus motif $D(x)_2DG(x)_2AR(x)_{7-12}G(x)_3D(x)_3D$ for this class of enzymes [15]. The ER membrane bilayer is shown as a green slab. *B*, Phosphatidylcholine (PC) synthesis and ER bilayer assembly (adapted from [26]). CEPT uses DAG and CDP-choline to form PC on the cytoplasmic leaflet of the ER membrane. A scramblase is needed to equilibrate newly synthesized PC between the two leaflets of the membrane bilayer. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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