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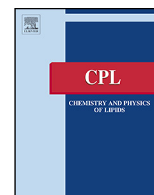

Disruption of lipid domain organization in monolayers of complex yeast lipid extracts induced by the lysophosphatidylcholine analogue edelfosine in vivo

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ABSTRACT

The lysophosphatidylcholine analogue edelfosine is a potent antitumor and antiparasitic drug that targets cell membranes. Previous studies have shown that edelfosine alters membrane domain organization inducing internalization of sterols and endocytosis of plasma membrane transporters. These early events affect signaling pathways that result in cell death. It has been shown that edelfosine preferentially partitions into more rigid lipid domains in mammalian as well as in yeast cells. In this work we aimed at investigating the effect of edelfosine on membrane domain organization using monolayers prepared from whole cell lipid extracts of cells treated with edelfosine compared to control conditions. In Langmuir monolayers we were able to detect important differences to the lipid packing of the membrane monofilm. Domain formation visualized by means of Brewster angle microscopy also showed major morphological changes between edelfosine treated versus control samples. Importantly, edelfosine resistant cells defective in drug uptake did not display the same differences. In addition, co-spread samples of control lipid extracts with edelfosine added post extraction did not fully mimic the results obtained with lipid extracts from treated cells. Altogether these results indicate that edelfosine induces changes in membrane domain organization and that these changes depend on drug uptake. Our work also validates the use of monolayers derived from complex cell lipid extracts combined with Brewster angle microscopy, as a sensitive approach to distinguish between conditions associated with susceptibility or resistance to lysophosphatidylcholine analogues.

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1. Introduction

Cellular membranes are complex assemblages of hundreds of different lipids and proteins. The biophysical properties of the various lipids and their phase behavior affect membrane fluidity, permeability and curvature, critically contributing to membrane function. The structure and composition of membranes in living cells is very dynamic and current models of membrane architecture comprise distinct organizational levels in all dimensions (Lingwood and Simons, 2010; van Meer et al., 2008; Simons and Ikonen, 1997; Rietveld and Simons, 1998). The plasma membrane of eukaryotes represents one of the most complex biomembranes featuring an asymmetric lipid distribution actively maintained across the bilayer as well as lateral domain organization within leaflets. Constitutive and agonist-stimulated synthesis and turnover of lipids maintain the required physical properties of the membrane and also store and release many bioactive molecules. Thus, regulation of local membrane organization through alteration of its lipid composition has functional consequences and provides a degree of versatility well-suited to fulfill the spatio-temporal requirements of cell signaling and trafficking pathways. In fact, a wide range of biological processes including cell proliferation, cell death, cell adhesion as well as pathological processes such as bacterial and viral infections depend on membrane organization that results from the biophysical

Abbreviations: BAM, Brewster angle microscopy; L_d, liquid disordered; L_o, liquid ordered; L_E, liquid expanded; ER, endoplasmic reticulum; PC, phosphatidylcholine; DAG, diacylglycerol.

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properties of specific lipids (van Meer et al., 2008; Ewers and Helenius, 2011; Lorizate and Krausslich, 2011; Wymann and Schneiter, 2008). Lipid structure determines their phase behavior in membranes. While lipids containing unsaturated hydrocarbon chains (like most glycerophospholipids found in biomembranes) are enriched in liquid-disordered phases (L_d), lipids with long, saturated hydrocarbon chains (like complex sphingolipids), tend to exhibit properties more similar to rigid phases. Furthermore, in the presence of sterols, sphingolipids have the capacity of forming a liquid-ordered phase (L_o) which has unique characteristics of being highly ordered but with superior translational mobility than a solid phase (van Meer et al., 2008). Biophysical studies performed using binary, ternary and quaternary lipid mixtures, support the notion of coexistence of immiscible phases in artificial membranes (van Meer et al., 2008; Rietveld and Simons, 1998; Collado et al., 2005; Prenner et al., 2007; Nathoo et al., 2013; Gröger et al., 2012; London, 2002; Veatch and Keller, 2005; Huang and Feigenson, 1999; Heberle et al., 2013; Feigenson, 2009; Betaneli et al., 2012; Arnold et al., 2005; Bastos et al., 2012; de Almeida et al., 2009; Matsumori et al., 2011; Jiang et al., 2014; Graber et al., 2012; Pan et al., 2013; Vega Mercado et al., 2012; Bagatolli and Needham, 2014). Applying this concept to membranes in living cells has fuelled exciting hypotheses on the functional consequences that lipid domain formation may have in cell physiology. The plasma membrane of eukaryotes is enriched in sphingolipids and sterols, and their interaction gives rise to membrane domains called "lipid rafts" that serve as platforms for association-dissociation of membrane proteins (Lingwood and Simons, 2010; Simons and Ikonen, 1997). These domains are characterized by tight packing of lipids and a high acyl chain order due to the enrichment in saturated and longer hydrocarbon chains and hydroxylated ceramide backbones (Lingwood and Simons, 2010). The concept of lipid rafts (Simons and Van Meer, 1988) has found many proponents (Brown and London, 1998a; Brown and London, 1998b; Pike, 2003; Pike, 2009), but since rafts are difficult to observe in living cells others have questioned their physiological relevance (Edidin, 2003; Munro, 2003; Kraft, 2013). Stable lipid domains that segregate proteins in live cells have been clearly imaged in yeast (Toulmay and Prinz, 2013; Ziółkowska et al., 2012; Spira et al., 2012).

A novel mode of action for an anti-cancer lipid drug through a specific modification of plasma membrane organization and perturbation of downstream signal transduction pathways has been proposed (Zaremberg et al., 2005; Gajate et al., 2004). Studies on the synthetic lysophosphatidylcholine analogue edelfosine, the prototype of the family of these anti tumour lipids, have shown that edelfosine affects membrane protein association with lipid rafts in tumoral cell lines, inducing apoptosis (Mollinedo et al., 2011; Wright et al., 2004; van der Luit et al., 2002). Structurally, edelfosine consists of an ether linked C18-hydrocarbon chain and a methyl group in positions *sn-1* and *sn-2* of the glycerol backbone respectively, and a phosphocholine headgroup in position *sn-3* (Fig. 1). The relatively large headgroup and the highly asymmetrical hydrocarbon tail region result in an "inverted cone" shape (also termed type I or positive curvature; Fig. 1) for this molecule (Cullis and De Kruijff, 1979; Cullis et al., 1986). Analysis of the phase behavior of edelfosine indicated the formation of non-lamellar assemblies such as interdigitated bilayers and micelles (Maurer et al., 1994), whereas its surface-active properties suggest that the drug can insert easily into cell membranes (Busto et al., 2007). Edelfosine can be co-dispersed in water with certain lipids (predominantly sterols, but also other "cone shaped" lipids (also termed type II or negative curvature) such as phosphatidic acid and diacylglycerol) to form stable liposomes (Fig. 1), based on structural complementation between sterols and edelfosine (Busto et al., 2008a) which could be a determinant of the cytotoxic effect of edelfosine. It has been suggested that the specific cytotoxicity of edelfosine is based on the preferential uptake into tumoral over normal cells which cannot incorporate enough ether lipid (Gajate et al., 2000). A current model of the mode of action of edelfosine

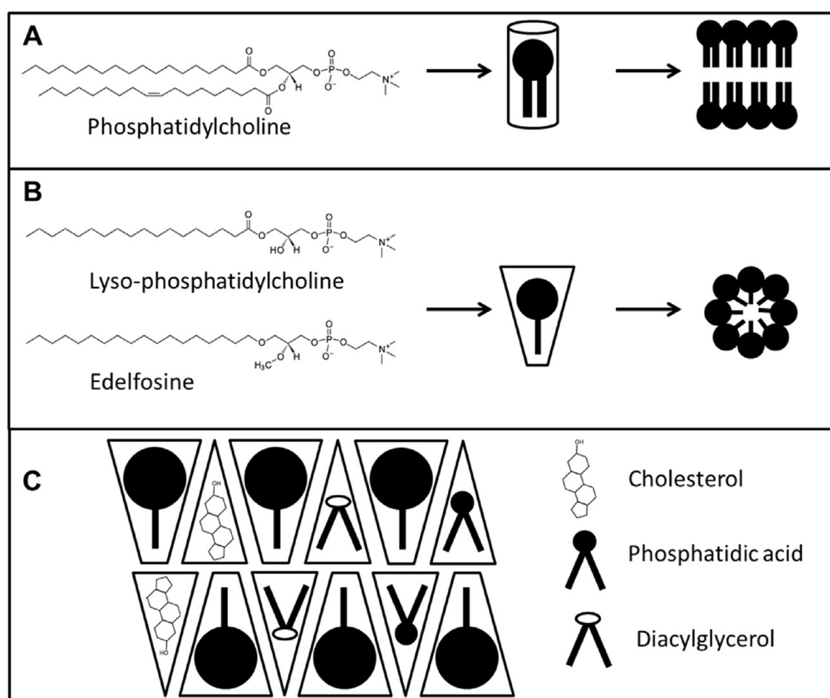

Fig. 1. Structure and geometry of phospholipids and lyso-lipid variants.
(A) The structure of phosphatidylcholine adopts bilayer phases due to the cylindrical molecular geometry. (B) The structures of lyso-phosphatidylcholine and edelfosine have an inverted cone geometry leading to the formation of non-lamellar phases. (C) The complementary geometries of edelfosine (inverted cone) with sterols, phosphatidic acid and diacylglycerol (cone) allow the formation of stable liposomes.

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