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Anti-Tumour Treatment

Cell membrane modulation as adjuvant in cancer therapy

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ABSTRACT

Cancer is a complex disease involving numerous biological processes, which can exist in parallel, can be complementary, or are engaged when needed and as such can replace each other. This redundancy in possibilities cancer cells have, are fundamental to failure of therapy. However, intrinsic features of tumor cells and tumors as a whole provide also opportunities for therapy. Here we discuss the unique and specific makeup and arrangement of cell membranes of tumor cells and how these may help treatment. Interestingly, knowledge on cell membranes and associated structures is present already for decades, while application of membrane modification and manipulation as part of cancer therapy is lagging. Recent developments of scientific tools concerning lipids and lipid metabolism, opened new and previously unknown aspects of tumor cells and indicate possible differences in lipid composition and membrane function of tumor cells compared to healthy cells. This field, coined Lipidomics, demonstrates the importance of lipid components in cell membrane in several illnesses. Important alterations in cancer, and specially in resistant cancer cells compared to normal cells, opened the door to new therapeutic strategies. Moreover, the ability to modulate membrane components and/or properties has become a reality. Here, developments in cancer-related Lipidomics and strategies to interfere specifically with cancer cell membranes and how these affect cancer treatment are discussed. We hypothesize that combination of lipid or membrane targeted strategies with available care to improve chemotherapy, radiotherapy and immunotherapy will bring the much needed change in treatment in the years to come.

Cellular membrane overview

The involvement of lipids in cell structures was first described in 19th century when Charles E. Overton postulate the lipid nature of cellular membranes. Lipids were considered as a cell wall component that maintains the aqueous cytoplasm separately from the extracellular medium. The earliest membrane organization models were postulated 30 years later, ranging from a monolayer to a trilayer of lipids and proteins [1,2], but the most accepted is the Fluid-mosaic model proposed by Singer and Nicolson in 1972 [3].

The fluid-mosaic model describes a bilayer of lipids in which some proteins are embedded, where lipids are free to rotate, move laterally or exchange between bilayers [4]. Some refinements have been added based on further research, such as the introduction of curvature and pore formation, membrane domains, a higher protein/lipid ratio and lipid interactions with cytoskeleton and surrounding matrix, which limit the freedom of the previous model considerably, but also adds complexity and increases functionality [1,2,4–6].

The cellular membrane is a fundamental cell component, not only due to the structural function but also regarding receptors, signaling, enzymatic activity, fusion–fission, endocytosis and transport among others, being responsible for interaction between cell and environment. Thus, research on membranes evolved in how to consider this cellular component, from a simple barrier between aqueous compartments to a more complex and fascinating structure with biological functions and an identity intrinsic to the type of cell or disease. The high lipid compositional complexity, versatility, interactions and distribution are related to concrete

Abbreviations: HMG-CoA reductase, 3-hydroxy-methylglutaryl CoA reductase; Emodin, 3-methyl-1,6,8-trihydroxyanthraquinone; CL, Cardiolipin; Cer, ceramide; Ch, cholesterol; DAG, Diacylglycerol; ER, endoplasmic reticulum; EGFR, epidermal growth factor receptor; EGCG, epigallocatechin gallate; FADD, Fas-Associated protein with Death Domain; So, gel solid-ordered state; GCS, Glucosylceramide synthase; IP3, inositol 1,4,5-triphosphate; IGF-1, insulin-like receptor; Ld, liquid-disordered state; Lo, liquid-ordered state; LPC, lyso-phosphatidylcholine; MβCD, methyl-beta-cyclodextrin; MUFA, monosaturated fatty acids; MDR, multidrug resistance; P-gp, P-glycoprotein; PA, phosphatidic acid; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PI, phosphatidylinositol; PS, phosphatidylserine; PUFA, polysaturated fatty acids; SCC, short chain ceramides; SL, sphingolipids; SM, sphingomyelin; SMase, sphingomyelinase; Tm, transition temperature.

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functions of the bilayer, determining the characteristics of the membrane or even cell. Lipid related studies revealed to be the key to better understand and comprehend the complexity of cellular mechanisms and related pathologies [2,7–11]. In that sense, new fields achieved importance such as cellular Lipidomics [12–15] or Membrane Biophysics [16–19]. In spite of solid awareness of lipid distribution, interactions and functionality, there is still a lot to learn in this respect.

Physical properties

Lipids are composed of a polar head and a relatively long hydrophobic tail. They tend to associate spontaneously in an aqueous medium due to thermodynamic forces, where hydrophobic tails are protected by a layer of hydrophilic heads, resulting in structures like micelles or bilayered sheets which are considered the origin of cell membranes [4,5].

The presence of hydrophobic and hydrophilic components allows non-covalent interaction with other lipids and proteins, conforming cellular and organelle membranes. Lipid type and distribution within a membrane is not homogeneous. Associations, enrichments and concrete lipid presence determine membrane functionality, showing the important role, often undervalued, of Lipidomics.

A well-known example is lipid asymmetry between inner and outer membrane leaflets. There is a phospholipid enrichment containing amine or serine moieties in the inner leaflet whereas choline and sphingomyelins (SM) are prevailing on the outside, as is shown in Fig. 1 [1,12].

Asymmetry maintenance is an active and energy dependent process which requires the involvement of enzymes such as flippases, scramblases and translocases [1,12,20]. The failure to preserve asymmetry is associated with apoptosis and pathological situations [1,7]. Thus, the exposure of phosphatidylethanolamine (PE) or phosphatidylserine (PS) in the external layer is related to an increase in aggregation and recognition by phagocytic cells, and reacts with molecules like Annexin in apoptotic assays [1,21]. Signaling lipids like phosphatidylinositol (PI) or phosphatidic acid (PA) are also enriched in the inner leaflet [7,12]. Due to asymmetry there is a negative inner membrane surface charge that influences hydrolysis of PI mediated by phospholipase C into inositol 1,4,5-triphosphate (IP3) and Diacylglycerol (DAG), known as second messenger molecules [11,22–24].

Finally, amine and serine moieties of the inner leaflet interact with the cytoskeleton, which forms fences or corrals that highly limits free lipid movement within the membrane and is involved in membrane curvature and in mechanical cell properties [1,21,25].

Lateral asymmetry is also widely reported resulting in polarization in some specialized tissues. In general it is assumed that apical areas are enriched in cholesterol (Ch) and sphingolipids (SL) contrary to basolateral areas, which present higher amount of phosphatidylcholine (PC) [25,26]. This distribution is required for barrier formation, transport and sensorial processes of intestinal epithelial cells among other examples [25–28].

On top of that, difference in membrane composition between organelles have been reported, explaining differences in function, strongly related with lipid synthesis. Endoplasmic reticulum (ER) is involved in the synthesis of glycerolipids and Ch, whereas the Golgi complex is where the synthesis of SM and glycosphingolipid takes place [12]. There is trafficking of lipids from these organelles to the membrane, resulting in a gradient of SL and Ch [29,30]. Thus, secretory organelles are 10-fold enriched in SL and Ch over the Golgi and ER [13]. Mitochondria are typically enriched in PE and Cardiolipin (CL) which has a bacterial origin [29], with low Ch content, whereas the ER presents higher amount of PC and PI [7,11,22].

Finally, lipid structure is involved in and affect curvature and distortion of membranes. Phospholipids like PC or SM present a cylindrical shape based on head and tail proportion, and due to their amphiphilicity, spontaneously form a bilayer in an aqueous environment (Fig. 2) [4,7,11]. Other lipids such as lysophosphatidylcholine (LPC) and polyphosphoinositides, for instance PIP2, have higher head to tail proportion and have an inverted cone-shape, which causes a membrane positive curvature. On the other hand PA, PE, PS, DAG, ceramides or CL are considered cone-shaped lipids for they present small heads and distort membranes with a negative curvature, as depicted in Fig. 2 [2,7,22,31,32]. Cone-shaped lipids may adopt non-bilayered, hexagonal and cubic, phases temporarily on which this mesomorphism gives a high versatility to the membrane [4,18,23,33]. These particular lipids influence the curvature of membrane, decreases energy required for fission, fusion, pore formation and vesicle trafficking, whereas also they regulate the activity of several relevant cell-signaling proteins [4,7,24,25]. Fusion, for example, is important in differentiation during embryogenesis and morphogenesis [34] and is involved in the fertilization process, when the membrane of spermatozoids, enriched in LPC, fuse with oocyte [20]. Particular lipids (PE, CL, PA) are recruited in cell or organelle membranes, which together with certain proteins coordinate with the cytoskeleton to carry on fusion and fission [25–27,32].

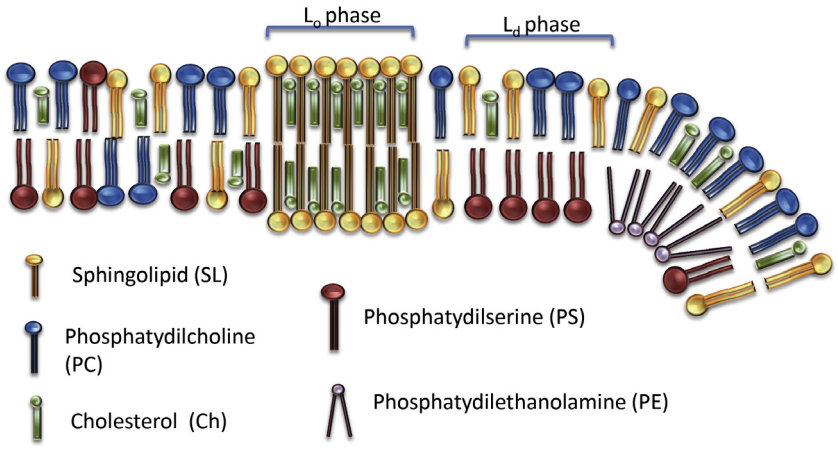

Fig. 1. Schematic representation of a cellular membrane depicting a selection of phospholipids as they appear in a bilayer. The liquid-ordered phase (Lo) typically harbors saturated phospholipids and cholesterol and therefore has a relatively rigid nature with a higher density of packing. The liquid-disordered phase is reached at temperatures above the transit temperature (Tm), which is typified by a more loose packing and less rigid nature.