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Review

Lipid rafts, KCa/ClCa/Ca^{2+} channel complexes and EGFR signaling: Novel targets to reduce tumor development by lipids?☆

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ABSTRACT

Membrane lipid rafts are distinct plasma membrane nanodomains that are enriched with cholesterol, sphingolipids and gangliosides, with occasional presence of saturated fatty acids and phospholipids containing saturated acyl chains. It is well known that they organize receptors (such as Epithelial Growth Factor Receptor), ion channels and their downstream acting molecules to regulate intracellular signaling pathways. Among them are Ca^{2+} signaling pathways, which are modified in tumor cells and inhibited upon membrane raft disruption. In addition to protein components, lipids from rafts also contribute to the organization and function of Ca^{2+} signaling microdomains. This article aims to focus on the lipid raft KCa/ClCa/Ca^{2+} channel complexes that regulate Ca^{2+} and EGFR signaling in cancer cells, and discusses the potential modification of these complexes by lipids as a novel therapeutic approach in tumor development. This article is part of a Special Issue entitled: Membrane channels and transporters in cancers.

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1. Introduction

Membrane lipid rafts are distinct plasma membrane nanodomains that are enriched with cholesterol, sphingolipids and gangliosides, with occasional presence of saturated fatty acids and phospholipids containing saturated acyl chains. In some rafts there are very high amount of ceramides instead of cholesterol [1,2]. It is well known that they organize receptors (such as Epidermal Growth Factor Receptor, EGFR), their downstream molecules to regulate intracellular signaling pathways, which may be inhibited upon membrane raft disruption. Lipid rafts have been implicated in the regulation of cell proliferation, apoptosis and cell migration suggesting first that alteration of these nanodomains could be involved in tumor development and second that their modification by lipids may become a novel and attractive strategy to reduce tumor development.

Lipid rafts provide signaling platforms for several growth factor receptors such as Human Epidermal growth factor Receptors (HERs), which are overexpressed in many cancers such as breast (for HER2) [3] and colon (for EGFR/HER1) [4] and participate in tumor development. Interestingly, the activation of EGFR generates intracellular Ca^{2+} variations, which by the formation of the Ca^{2+}/CaM complex also control EGFR activities [5]. Ca^{2+} homeostasis is regulated by Ca^{2+} channels, and during the last decade, these channels and Ca^{2+}-activated K^+ channels (KCa) and Ca^{2+}-activated Cl^- channels (ClCa) were found to be expressed in various tumors. Their physiological function is hijacked by the cancer cell to drive essential biological functions for tumor development such as cell proliferation and cell migration [6–10]. For reducing energy consumption and for the fine regulation of their activities, Ca^{2+}, KCa and ClCa channels appear to be associated as complexes in cancer cells and contribute to cancer associated functions such as cell proliferation, cell migration and the capacity to develop metastases [11]. Thus, we propose that these complexes are spatially segregated in nanodomains such as lipid rafts. This particular localisation has been observed for the TRPC1 channelosome [12], and many ion channels are found to be expressed in lipid rafts [13]. Nevertheless, the specific localization and regulation of Ca^{2+}, KCa and ClCa channels alone or as complexes in lipid rafts need to be addressed in tumor cells.

The role of lipid rafts in tumor cells has been recently reviewed [14]. The present article aims to focus on the lipid raft KCa/ClCa/Ca^{2+} channel complexes and EGFR signaling in cancer cells and on the potential modification of these complexes by lipids as a novel therapeutic approach in tumor development.

2. Lipid rafts

Lipid rafts are defined as nanodomains within the lipid bilayer [2]. Raft domains lead to protein and lipid compartmentalization inside the plasma membrane. These highly dynamic structures act as signaling platforms and coordinate transduction pathways. They are also involved in endocytosis, protein trafficking and adherens junctions (see for reviews [15–17]). The lipid raft composition is distinct from the non-raft domain in cholesterol, glycosphingolipids, sphingolipids, gangliosides, with occasional presence of saturated fatty acids and phospholipids containing saturated acyl chains and loss of glycerolipids, omega 3 fatty acids and phosphatidylethanolamine. In some rafts there are very high amounts of ceramides instead of cholesterol [1]. Biochemical techniques have allowed to isolate the lipid rafts using their resistance to solubilization by cold nonionic detergents such as Triton X-100 [18]. Cholesterol-rich rafts can be separated from non-raft domains by sucrose gradient centrifugation thanks to their lower density. More recently, microscopy and spectroscopy techniques have allowed to directly visualize the lipid raft structure [19], and proteomic profiles of membrane fractions from normal and cancerous human tissues are henceforth available using labeling mass spectrometry [20]. Two types of lipid rafts can be distinguished: caveolae and non-caveolae (Fig. 1). Caveolae contains caveolin which is a cholesterol anchoring protein and a specific scaffolding protein creating plasma membrane invagination [21]. In addition to be enriched with cholesterol and sphingolipids, caveolae also contain a variety of fatty acids highly enriched with saturated fatty acids, and caveolin-1 (Cav-1) acylated by palmitic acid and stearic acid [22]. This acetylation of Cav-1 may play a pivotal role in subcellular location including targeting to caveolae. Indeed, Cav-1 has been described as forming mobile signaling platforms within the caveolae by sequestration of multiple proteins through interaction via the scaffolding domain within the NH_2 terminus. In most cases, the interaction with Cav-1 either maintains the signaling protein in an inactive state until a stimulus is presented (as observed for BKCa/KCa1.1, TRPC, and EGFR, see below) or terminates signal transmission after activation. Caveolae could also form junctional complexes that couple the plasma membrane and the endoplasmic reticulum necessary for Ca^{2+} signaling. For example, this junctional complex is required for store-operated Ca^{2+} entry (SOCE) and for the coupling between BKCa channel and IP3 receptor (IP3R). On the other hand, non-caveolar rafts are enriched in flotillin. After oligomerization, flotillin anchors to the plasma membrane via myristoylation and palmitoylation sites. Unlike caveolae, the microdomains are laterally mobile within the membrane. They appear to bud into the cell and form planar lipid rafts, unlike plasma membrane invagination as observed for caveolar rafts (for review [15]).

The protein and lipid composition of rafts is dramatically altered in cancer and impacts kinase activity, protein trafficking, adhesion and apoptosis [17]. Lipid raft-dependent signaling pathways are often hyperactivated in cancer and implicated in signal deregulation [23]. Oncogenicity of Akt (protein kinase B) arises from the activation of both proliferative and anti-apoptotic signaling routes. Furthermore, Akt contributes to tumor progression by promoting cell invasiveness and angiogenesis [24,25]. Hyperactivated Akt in primary tumors is considered to be a negative prognostic marker for disease outcome [26]. Membrane recruitment is crucial for Akt activation and its membrane localization protects Akt from inactivation by phosphatases [25]. This observation is in agreement with the lipid hypothesis that raft environment controls/regulates protein signaling complexes. Elevated levels of lipid rafts in cancer cells [27], which are specially enriched with inositols [28–30], have been related with oncogenesis by promoting overactivation of the Akt signaling pathway [31]. For example Akt activation is promoted by lipid rafts in colon, melanoma and prostate cancer cells [32–34].

CD95 is a well-known death receptor, and its proper function is essential for the elimination of viral or transformed cells [35]. Death pathway signaling has been related with lipid rafts, including death-receptor-mediated signaling pathways [36,37]. The partitioning of both CD95L and CD95 into rafts is necessary for cell death signal transduction [35–39], promoting an efficient CD95–CD95L interaction and initiating apoptosis [37,39,40]. However, recruitment and aggregation of CD95 in lipid raft clusters have been shown independent of its ligand CD95L [41]. In fact CD95 redistribution into lipid rafts can be stimulated not only by CD95L, but also by drugs that have the potential to mimic a