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Lipid rafts as major platforms for signaling regulation in cancer

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A B S T R A C T

Cell signaling does not apparently occur randomly over the cell surface, but it seems to be integrated very often into cholesterol-rich membrane domains, termed lipid rafts. Membrane lipid rafts are highly ordered membrane domains that are enriched in cholesterol, sphingolipids and gangliosides, and behave as major modulators of membrane geometry, lateral movement of molecules, traffic and signal transduction. Because the lipid and protein composition of membrane rafts differs from that of the surrounding membrane, they provide an additional level of compartmentalization, serving as sorting platforms and hubs for signal transduction proteins. A wide number of signal transduction processes related to cell adhesion, migration, as well as to cell survival and proliferation, which play major roles in cancer development and progression, are dependent on lipid rafts. Despite lipid rafts harbor mainly critical survival signaling pathways, including insulin-like growth factor I (IGF-I)/phosphatidylinositol 3-kinase (PI3K)/Akt signaling, recent evidence suggests that these membrane domains can also house death receptor-

Abbreviations: APL, alkylphospholipid analogue; CASMER, cluster of apoptotic signaling molecule-enriched rafts; DED, death effector domain; DD, death domain; DISC, death inducing signaling complex; DR, death receptor; DRM, detergent-resistant membrane; FADD, Fas-associated death domain protein; HMG-CoA, 3-hydroxy-3-methyl-glutaryl CoA; IGF, insulin-like growth factor; IGFBP, IGF binding receptor; IGF-I, insulin-like growth factor I; IGF-IR, IGF-I receptor; IR, insulin receptor; IRS-1, insulin receptor substrate-1; MAPK, mitogen-activated protein kinase; MCL, mantle cell lymphoma; MM, multiple myeloma; mTOR, mammalian target of rapamycin; PDK1, phosphatidylinositol-dependent protein kinase 1; PH, pleckstrin homology domain; PI3K, phosphatidylinositol 3-kinase; PIP2, phosphatidylinositol-4,5-bisphosphate; PIP3, phosphatidylinositol-3,4,5-trisphosphate; TNF, tumor necrosis factor; TRAIL, tumor necrosis factor (TNF)-related apoptosis-inducing ligand.

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mediated apoptotic signaling. Recruitment of this death receptor signaling pathway in membrane rafts can be pharmacologically modulated, thus opening up the possibility to regulate cell demise with a therapeutic use. The synthetic ether phospholipid edelfosine shows a high affinity for cholesterol and accumulates in lipid rafts in a number of malignant hematological cells, leading to an efficient *in vitro* and *in vivo* antitumor activity by inducing translocation of death receptors and downstream signaling to these membrane domains. Additional antitumor drugs have also been shown to act, at least in part, by recruiting death receptors in lipid rafts. The partition of death receptors together with downstream apoptotic signaling molecules in membrane rafts has led us to postulate the concept of a special liquid-ordered membrane platform coined as "**c**luster of **a**poptotic **s**ignaling **m**olecule-**e**nriched **r**afts" (CASMER), referring to raft platforms enriched in apoptotic molecules. CASMERs act as scaffolds for apoptosis signaling compartmentalization, facilitating and stabilizing protein–protein interactions by local assembly of cross-interacting molecules, which leads to apoptosis amplification and a decrease in apoptotic signal threshold. Edelfosine also displaced survival PI3K/Akt signaling from lipid rafts, leading to Akt inhibition, in mantle cell lymphoma cells. Thus, membrane rafts could act as scaffold structures where segregation of pro-from anti-apoptotic molecules could take place. In this review, we summarize our view of how reorganization of the protein composition of lipid raft membrane domains regulates cell death and therefore it might be envisaged as a novel target in the treatment of cancer.

Introduction

Plasma membrane is essential for the life of a cell by constituting a barrier for most substances that separates the intracellular milieu and living material within the cell from the non-living environment. The establishment of a boundary that separates the interior of a cell from the environment is critical for all types of life from the simplest to the most complex, and this compartmentalization enables chemical reactions to take place that would otherwise be impossible. Eukaryotic cells can also compartmentalize molecules inside organelles and the membranes that surround the nucleus and other cellular particulates share a lot of properties with the plasma membrane. However, cell membrane does not act entirely as an impermeable barrier, and it determines what gets in and out of the cells as well as it controls how substances, and what type of compounds, can move in and out of the cell. In this way, the plasma membrane allows some molecules to be concentrated inside the cells. In addition, not only do plasma membranes separate the inside and outside of a cell, but they receive signals from either outside and inside the cells, interpret and transduce these signals leading to a cell response. Cell membrane is made mainly of lipids that were long believed to be in a disorder fluid state, where proteins were supposed to move freely within this kind of lipid sea, thus leading to the fluid mosaic model introduced by Seymour Jonathan Singer and Garth L. Nicolson in 1972 (Singer and Nicolson, 1972). However, more ordered membrane domains arise in the presence of some membrane-active sterols, most importantly cholesterol and its analogues in other organisms, which have led to the concept of lipid raft membrane microdomains (Simons and Ikonen, 1997) that postulated the presence of lipid rafts as more ordered and tightly packed structures than the surrounding lipid bilayer and that move freely within the liquid-disordered cell membrane. An increasing number of proteins involved in signal transduction have been found to locate in these more ordered membrane domains, and thereby these lipid rafts would function as platforms for the recruitment of signaling

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