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Review

Dissecting lipid raft facilitated cell signaling pathways in cancer

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Abstract

Cancer is one of the most devastating disorders in our lives. Higher rate of proliferation than death of cells is one of the essential factors for development of cancer. The dynamicity of cell membrane plays some vital roles in cell survival and cell death, including protection, endocytosis, signaling, and increases in mechanical stability during cell division, as well as decrease of shear forces during separation of two cells after division, and cell separation from tissues for cancer metastasis. Within the membrane, there are specialized domains, known as lipid rafts. A raft can coordinate various signaling pathways. Recent data on the proteomics of lipid rafts/caveolae have highlighted the enigmatic role of various signaling proteins in cancer development. Analysis of these data of raft proteome from various tumors, cancer tissues, and cell lines cultured without and with therapeutic agents, as well as from model rafts revealed that there may be two subsets of raft assemblage in cell membrane. One subset of raft is enriched with cholesterol–sphingomyeline–ganglioside–cav-1/Src/EGFR (hereafter, "chol-raft") that is involved in normal cell signaling, and when dysregulated promotes cell transformation and tumor progression; another subset of raft is enriched with ceramide–sphingomyeline–ganglioside–FAS/Ezrin (hereafter, "cer-raft") that generally promotes apoptosis. In view of this, and to focus insight into the cancer cell physiology caused by the lipid rafts mediated signals and their receptors, and the downstream transmitters, either proliferative (for example, EGF and EGFR) or death-inducing (for example, FASL and FAS), and the precise roles of some therapeutic drugs and endogenous acid sphingomylenase in this scenario in in situ transformation of "chol-raft" into "cer-raft" are summarized and discussed in this contribution.

Keywords: Cancer; Catenin; Caveolin-1; CD44; Ceramide; EGFR; Cholesterol; E-cadherin; Ezrin; FAS/CD95; FASL; Focal adhesion kinase; H-ras; Integrin; Lipid rafts; Matrix metalloproteinases (MMPs); Proteomics; Signal transduction; Sphingomyelin; uPA; uPAR; MAP kinase

Contents

Abbreviations: Acid sphingomyelinase, ASMase; Activator protein-1, AP-1; Caveolin-1, cav-1; Ceramide, Cer; Cholesterol, Chol; Extracellular matrix, ECM; E-cadherin, E-cad; Endoplasmic reticulum, ER; Epidermal growth factor, EGF; EGF receptor, EGFR; Extracellular signal-regulated kinase, ERK; FAS antigen, FAS; FAS associated death domain, FADD; FAS ligand, FASL, Death-inducing signaling complex, DISC; Focal adhesion kinase, FAK; Glycosyl phosphatidyl inositol, GPI; Insulin like growth factor, IGF; Matrix metalloproteinases, MMPs; Mitogen activated protein kinase, MAPK; MAP/ERK kinase 1/2, MEK1/2; Nuclear factor-kB, NF-kB; Phosphoinositide 3-kinase, PI3K; Plasma membranes, PM; Receptor tyrosine kinases, RTKs; Retinoic acid, RA; RA receptor, RAR; Sentinel lymph nodes, SLN; Sphingomyelin, SM; Thrombospondine 2, THBS2; Urokinase type plasminogen activator (uPA); uPA receptor (uPAR)

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1. Introduction

Maintenance of balance between cell proliferation and cell death is the main key of normal development. Cancer cells have higher rate of proliferation than death. Usually, deregulated cell cycle is the cause of such impairment. Deregulation of cell cycle is caused by aberrant signaling. The dynamicity of membranes and flip-flop flexibility of lipids within cell membrane play some vital roles in cells life and death. Plasma membrane gives a protection to cytoplasmic ingredients and organelles, it perform endocytosis and signaling, and increases the mechanical stability of cells during division, as well as the flexibility of lipids within the membrane causes decrease of shear forces during cell separation (for example, separation of individual cells from the host tumor during cancer metastasis). Within the membrane, there are specialized domains, known as lipid rafts. Many proteins of receptor tyrosine kinases (RTK) family members, including epidermal growth factor receptor (EGFR), and other proteins, including caveolin-1, CD44, uPAR, H-Ras, integrins and catenins have been implicated to various cellular functions, including stability and signaling. Some of these proteins precisely exhibit their function through lipid rafts, either structurally or functionally, or both, in immune signaling, angiogenesis, cell polarity and cancer progression. Function of proteins like, FAS and FASL virtually remain inert, which in turn facilitate tumor development by reduced rate of apoptosis. Also, impaired function of FAS and FASL results in tumor development, immune disorders and other diseases, including diabetes and Parkinson's disease. Investigations on the molecular mechanisms of cell transformation and development of various cancers, including breast, lung, prostate, gliomas and multiple sarcomas are given immense importance, since cancer is one of the major threats in our life. We have been working for years on molecular and epigenetic regulation of cancer, including lipid rafts, DNA methylation, and lipid rafts and cancer metastasis [1]. In this contribution, I shall discuss some important signaling events leading to cell transformation and cancer progression, which otherwise depend predominantly on lipid rafts. A handfull collective knowledge of lipid rafts and raft-assisted signaling pathways would help us to choose strategies for prevention, cure and better management of cancers using natural compounds, synthetic inhibitors, radiation or other forms of therapies.

1.1. The flora and fauna of lipid rafts

Lipid/membrane rafts are small (10–200 nm), heterogeneous, highly dynamic, sterol- and sphingolipid-enriched domains that compartmentalize cellular processes. Caveolae, a subclass of rafts, are characterized by flask-like invaginations of the plasma membrane that are distinguished from bulk lipid rafts by the presence of caveolin-1 (cav-1). Hence, lipid rafts/caveolae are specialized molecular assemblages of sphingolipids and cholesterol, orchestrated by proteins and gangliosides that are known principally for their pivotal role in trans-cytosis, sorting of sphingolipids and cholesterol in the cell, and as platforms to concentrate receptors and assembling the signal transduction machinery; but their ability to influence the actin cytoskeleton, cell polarity, angiogenesis, membrane fusion is probably just as significant [1–20]. Fig. 1. shows a schematic view of lipid rafts, and caveolae like compositions. The lower half of the Fig. 1 depicts a typical composition of a cell death associated raft clustering enriched with ceramide (will be discussed below). All the components (lipids and proteins) presented in Fig. 1 are not available in the same type of raft. The raft composition largely depends on what fraction of lipids in the cytoplasmic leaflet form rafts in living cells and the type of cellular response after receiving signal/stimuli [2–31]. All tumor cells shed plasma membranes enriched in sphingomyelin (SM), cholesterol and gangliosides to counter possibly against hosts immune responses and keep themselves free from destruction by immune system (reviewed in ref. [1], see also [28–32]).

The lipid raft proteomics is the study of all the proteins that use, and most importantly need raft assemblage for their proper functioning, certainly expressed by a given cell, tissue or organism at a given time and under specific conditions. Some of those proteins are well illustrated in the case of signaling in hematopoietic cells, including T-cells and B-cells, in a variety of cancer cells and to some extent in model rafts [1–17,19–26,33–53]. The binding of actin is an important example of interaction of raft components with cytoplasmic proteins, which implies raft mediated signaling, cell surface organization and a role for rafts in mechanical properties of cell membranes. Actin forms protein-chains such as Cadherin–Catenin–Actin, CD44–(Ezrin, Radixin, Moesin; ERM)–Actin, and some others depending on tissue and cell types where catenin and ERM-like proteins constitute a