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Rafting Down the Metastatic Cascade: The Role of Lipid Rafts in Cancer Metastasis, Cell Death, and Clinical Outcomes

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ABSTRACT

Lipid rafts are tightly packed, cholesterol- and sphingolipid-enriched microdomains within the plasma membrane that play important roles in many pathophysiologic processes. Rafts have been strongly implicated as master regulators of signal transduction in cancer, where raft compartmentalization can promote transmembrane receptor oligomerization, shield proteins from enzymatic degradation, and act as scaffolds to enhance intracellular signaling cascades. Cancer cells have been found to exploit these mechanisms to initiate oncogenic signaling and promote tumor progression. This review highlights the roles of lipid rafts within the metastatic cascade, specifically within tumor angiogenesis, cell adhesion, migration, epithelial-to-mesenchymal transition, and transendothelial migration. In addition, the interplay between lipid rafts and different modes of cancer cell death, including necrosis, apoptosis, and anoikis, will be described. The clinical role of lipid raft–specific proteins, caveolin and flotillin, in assessing patient prognosis and evaluating metastatic potential of various cancers will be presented. Collectively, elucidation of the complex roles of lipid rafts and raft components within the metastatic cascade may be instrumental for therapeutic discovery to curb prometastatic processes.

Introduction

The presence and dynamic clustering of sphingolipid- and cholesterol-enriched "raft" domains within the plasma membrane were postulated in 1997 by Simons and Ikonen (1). This discovery added complexity to the "fluid mosaic" model presented by Singer and Nicolson, which postulated that phospholipids and membrane proteins exhibited random lateral organization within a fluid lipid bilayer (2). Lipid rafts are small arrangements enriched in specific lipids (such as saturated sphingolipids) and proteins [namely glycosylphosphatidylinositol (GPI)-anchored proteins], and the term is intended to convey the lateral heterogeneity that exists in cellular membranes (3). Elevated concentrations of cholesterol and sphingolipids containing saturated hydrophobic chains allow for more densely packed, ordered lipid arrangements, in comparison with the surrounding bilayer (4). Cholesterol, in particular, acts as both a glue and a spacer between nonpolar regions of saturated lipids, and its presence has proven vital for raft assembly and integrity. Lipid rafts have more recently been defined as transient and dynamic, both in terms of their lateral fluidity within the membrane and their constant flux of assembly/disassembly (3). The dynamic nature of rafts is highlighted by spatiotemporal changes of area and continuity between raft and nonraft regions as a result of cellular processes and stimuli. Heterogeneity also exists within lipid rafts between inner and outer leaflets of the lipid bilayer, governing biophysical properties of cellular membranes, such as curvature and rigidity, while also influencing the formation of vesicles for endo- and exocytosis (5).

The dynamic nature of lipid rafts along with their small size, short lifetime, and nonbinary characterization of "raft" and "nonraft" regions confound their experimental observation (3). The presence of heterogeneous lipid microdomains within cellular plasma membranes has been demonstrated as early as 1982, through the use of fluorescence lifetime decay of 1,6-diphenyl-1,3,5-hexatriene (6). Evidence of lipid raft microdomains was further supported by discovery of high cholesterol and glycosphingolipid regions that remained insoluble in cold, nonionic detergents (7). While detergent insolubility is still commonly used to isolate lipid rafts, validation of fluorescently labeled probes and advances in super resolution microscopy have allowed for direct visualization of raft composition, previously unseen using conventional confocal microscopy (3, 8, 9). Mass spectrometry is used to detail protein and lipid composition of raft domains, while Förster resonance energy transfer has been instrumental in probing raft presence and size (3). What remains a challenge, and what makes rafts somewhat controversial, are a lack of modalities for both live cell and *in vivo* observation over extended periods. Nonetheless, advances in *in vitro* observation and characterization reinforce their importance in cellular biology.

Lipid rafts can exist in either nonplanar (invaginated) or planar (flat) configurations (10). Caveolins are associated proteins of nonplanar lipid rafts, and are critical structural components of invaginated microdomains within the plasma membrane, known as caveolae (11). There are three known isoforms in the caveolin family; caveolin-1 and caveolin-2 are expressed ubiquitously and abundantly in epithelial cells, while caveolin-3 is highly expressed in striated and smooth muscle cells (12). On the contrary, planar rafts are smaller and remain as flat, ordered structures that are abundant in flotillin proteins (flotillin-1 and flotillin-2; refs. 1, 10). Flotillin proteins are indispensable structural components to non-caveolae planar rafts and also function as signaling platforms in the compartmentalization of membrane receptors (13).

Lipid rafts play a vital role in receptor trafficking and signal transduction, largely through their capacity to act as concentrating platforms, prompting unique interactions between clustered

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proteins (14). Through coalescing certain proteins, kinases, and phosphatases, while excluding others, a new lipid membrane environment is created. For example, lipid rafts protect receptors from enzymatic degradation or inactivation from non-raft enzymes. Specific receptors are predisposed to raft translocation, juxtaposing monomers to promote receptor oligomerization and supramolecular clustering, which in turn amplifies downstream signaling (15). This combination of signaling molecule concentration and exclusion of unwanted modulators make rafts master regulators of signal transduction. Within the context of cancer, these mechanisms of raft-mediated signal augmentation have been implicated in oncogenic and prometastatic signaling pathways (16). This review summarizes the roles that lipid rafts play within cancer metastasis, cell death, and raft-associated clinical biomarkers.

Lipid Rafts in Cancer Metastasis

The metastatic dissemination of cancer cells from the primary tumor to distant organs is a process that few cells survive (17). Successful metastatic colonization requires the following: creation of tumor neovasculature to support nutrient and oxygen demand, enhanced cellular motility through an epithelial-to-mesenchymal transition (EMT), directed migration and transendothelial migration (TEM) into the vasculature, survival of aberrant shear conditions in circulation, endothelial rolling and extravasation, and a phenotypic switch back to a proliferative state. Despite its inefficiencies, metastasis is responsible for approximately 90% of all cancer-related deaths (18). Understanding the complex protein interactions that allow for successful dissemination of specific subpopulations of cells is critical for discovery and development of antimetastatic therapies. Herein, the roles of lipid rafts within the steps of cancer metastasis will be discussed (**Table 1A**) and illustrated (**Fig. 1**).

Angiogenesis

Lipid rafts play an important role in angiogenic signaling, as demonstrated in studies of raft antagonization. One study found that treatment with cerivastatin, an inhibitor of cholesterol biosynthesis, which disrupts lipid rafts, attenuated angiogenesis by inhibiting endothelial cell migration and capillary formation (19). Another study found that raft disruption in triple-negative breast cancer (TNBC) cells via the cholesterol-depleting agent, methyl-beta-cyclodextrin (mβCD), inhibited angiogenic signaling through the suppression of proangiogenic markers, namely tyrosine protein kinase receptor (20). Likewise, conditioned media from mβCD-treated cancer cells decreased endothelial branching and capillary structures, demonstrating the obligatory roles of lipid rafts in tumor angiogenesis (21). Lipid rafts have also been found to mediate and activate heparinase-induced protein kinase B (Akt/PKB) phosphorylation, a proangiogenic response in hypervascularized tumors (22).

The VEGF/VEGFR2 axis is a proangiogenic signaling pathway employed by cancer cells via enhanced VEGF secretion (23). Lipid rafts have proven to be important in endothelial cell VEGFR2 functionality. For example, one study found that affecting endothelial cholesterol homeostasis via liver X receptor activation impaired VEGFR2 compartmentalization in lipid rafts, leading to defective VEGFR2 phosphorylation and downstream signaling upon VEGF-A stimulation (24). Another study found that lipid raft marker caveolin-1 secreted by metastatic prostate cancer cells, potentiated angiogenic signaling though colocalization and autophosphorylation of endothelial cell VEGFR2 (25). Moreover, a separate study found that by inhibiting CD82 internalization and distribution into lipid rafts, VEGFR2 phosphorylation was reduced, attenuating angiogenic signaling (26).

Lipid rafts not only play a role in receptor signaling, but in cancer cell–secreted VEGF as well. Lipid raft–localized Hsp90 was found to stabilize CD24, necessary for STAT3 activation and VEGF angiogenic signaling in colorectal cancer cells (27). Lipid rafts are also involved in exosome uptake, enabling noncoding miRNA communication between cancer cells, the endothelium, and stroma (28). One study found that endothelial cell internalization of ovarian cancer–derived exosomal miR-205 occurred in a lipid raft–dependent manner. Inhibition of lipid raft–mediated endocytosis curbed miR-205 uptake, thereby inhibiting angiogenesis (29). These studies demonstrate specific instances of raft-promoted tumor angiogenesis, making cholesterol modulation an appealing target to prevent tumor vascularization.

EMT

Lipid raft disruption has been shown to attenuate EMT in cancer. One study found that disrupting lipid rafts with simvastatin suppressed integrin-β3/FAK signaling, reversing EMT and EMT-associated paclitaxel resistance in non–small cell lung cancer (NSCLC) cells (30). Another study found that nystatin, a cholesterol sequestering agent, suppressed EMT markers in gastric cancer cells (31). They further demonstrated that CXCL12/CXCR4-induced mesenchymal-to-epithelial transition factor (c-MET) activation and EMT are dependent on lipid raft caveolin-1 signaling. Nystatin treatment also attenuated EMT by disrupting TGFβ signaling (32), which is strongly implicated in EMT and enhanced cancer cell motility (33). Cholesterol was found to be essential for the TGFβ receptor activation of MAPK and subsequent EMT induction (32). This TGFβ–EMT synergy was contingent upon TGFβ receptor localization into lipid rafts for efficient downstream signaling. Osthole, another lipogenic modulator, inhibits EMT via lipid raft depletion. A study found that osthole suppressed the hepatocyte growth factor/c-Met signaling pathway in breast cancer cells, abrogating a mesenchymal phenotype through downregulation of vimentin and upregulation of E-cadherin (34). Meanwhile, another study found that localization of the EMT-promoting glycoprotein, podoplanin, into lipid raft domains was necessary for podoplanin-mediated EMT and cell migration (35). Treatment with mβCD impaired podoplanin lipid raft compartmentalization and impeded EMT.

The flotillin and caveolin families of proteins are also important drivers of EMT. One study found that upregulation of caveolin-1 is associated with enhanced EMT and aggressive, metastatic bladder cancer (36). Caveolin-1 enhanced EMT by upregulating Slug, an EMT promoting transcription factor, through PI3K/AKT signaling. Knockdown of caveolin-1 reduced Slug expression, subsequently inhibiting EMT. Likewise, flotillin-2 is upregulated in gastric cancer cells and is required for TGFβ-induced EMT (37). Inhibition of flotillin-2 reduced EMT markers, vimentin and N-cadherin.

While much work has shown that disrupting lipid rafts prevents EMT signaling, other research shows that lipid raft destabilization is required for EMT. One study found that lipid raft stability decreases during EMT in breast cancer cells (38). Stabilizing lipid rafts with docosahexaenoic acid (DHA) abrogated EMT hallmarks, prevented mesenchymal signaling, and inhibited metastasis. This demonstrates the complex interplay between rafts and EMT, warranting further validation before clinical implementation of raft destabilizers.

Migration

Because lipid rafts are closely tied to cytoskeletal components and receptor signaling, many studies have looked at their role within focal

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Table 1A. Lipid rafts in metastatic stages, including angiogenesis, EMT, cell migration, TEM, and cell adhesion, along with mechanisms of cell death, including necrosis, apoptosis, and anoikis.

	Important proteins/pathway	Lipid rafts effect on stage	Cell lines	Lipid raft treatment	References
Angiogenesis	TEK, RhoA	Promote	MDA-MB-231, MDA-MB-468, ZR 751, HUVECs, HMEC	Cerivastatin, mβCD, nystatin, and filipin III (inhibitors)	(19–21)
	VEGF/VEGFR2 *Caveolin-1, CD82, CD24/Hsp90/STAT3*	Promote	PC-3, LNCaP, LLC-1, HT-29, SW-480, HUVECs	*CAV1* siRNA	(24–27)
	Exosomal miR-205	Promote	HO-8910, SKOV-3	Filipin III, simvastatin (inhibitors)	(29)
EMT	**TGFβ/MAPK** *ERK, p38*	Promote	HaCaT, NMuMG	Nystatin	(32)
	Integrin-β3 *pFAK/pAkt/pERK/TGF-β*	Promote	A549, PC-9	Simvastatin	(30)
	HFG/c-Met *pAkt, mTOR*	Promote	MCF7, MDA-MB-453, MDA-MB-231, BT-20	Osthole (inhibitor)	(34)
	Podoplanin *ROCK/ezrin/radixin/moesin*	Promote	MDCK type II	mβCD	(35)
	Caveolin-1/c-MET *CXCL12/CXCR4, Slug, PI3K/Akt*	Promote	T24, UMUC3, HT1376, 5637, MGC-803, SGC-7901, BGC-823	*CAV1* siRNA, nystatin	(31, 36)
	Flotillin-2 *TGFβ/vimentin/N-cadherin*	Promote	GES-1, SGC-7901, NCI-N87, MGC-803	Flotillin-2 siRNA	(37)
	Snail, Slug	Inhibit	MDA-MB-231	DHA (lipid raft stabilizer)	(38)
Migration	**Integrin-β1/MMP-9/uPAR** *Src, FAK, Cav, Akt, ERK*	Promote	P29, MDA-MB-231, ZR-751, HMEC	mβCD, nystatin	(21, 44)
	EGFR *Akt/PKB*	Promote	MDA-MB-231, MCF7, T47D	mβCD	(50)
	CD133/Caveolin-1 *FAK, NF-κB*	Promote	MIA PaCa-2, Panc-1, SU.86.86	Lovastatin (inhibitor), *CAV1* siRNA	(54)
	Flotillin-2 *PI3K/Akt*	Promote	MDA-MB-231, MCF7	Flotillin-2 shRNA	(52, 53)
	SK3/Orai1 *Calpain/talin*	Promote	MDA-MB-435	Alkyl-lipid ohmline (inhibitor)	(42)
	Squalene synthase/TNFR1 *MMP1/NF-κB*	Promote	A549, CL1–5	mβCD	(45)
	CXCL12/CXCR4 *Caveolin-1/C-met, EGFR, $G_{\alpha i}$/HER2/Src, PI4KIIIα*	Promote	C4-2B, LNCaP, PC3, MGC-803, SGC-7901, BGC-823	Nystatin, CAV1 siRNA	(31, 48, 49)
	Artificial crosslinking of GPI-anchored placental alkaline phosphatase	Promote	A375, HeLa	Ru-complex–based trefoil molecule	(41)
	TRPM8/AR *FAK*	Promote	PC3, LNCaP		(51)

(Continued on the following page)

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	Important proteins/pathway	Lipid rafts effect on stage	Cell lines	Lipid raft treatment	References
TEM	**C1QBP/CD44vg** *IGF-1R/PI3K/MAPK*	Promote	H MIA-PaCa-2, PANC-1, SW1990, Capan-1, BxPC-3		(58)
	Caveolin-1/MT1-MMP *PI3K/Akt/mTOR*	Promote	MDA-MB-231, T47D, BT549, Hs578T, MDA-MB-453, SK-BR-3	mβCD, CAV1 siRNA, nystatin	(64, 65)
	Caveolin-1/FAPα	Promote	CAFs		(63)
	Podoplanin *RhoC-GTPase/ROCK/LIMK/Cofilin*	Promote	HaCaT, SCC29, A253, Fadu, HN30, SCC13, HN5	mβCD	(66)
Adhesion	Fibronectin and vitronectin adhesion	Promote	MDA-MB-231, MDA-MB-468	mβCD	(20)
	Integrin-β1/focal adhesion complex proteins	Promote	MDA-MB-231, HeLa, HSC5, HepG2, HCT-116	mβCD, simvastatin, emodin, gambogic acid (inhibitors)	(40, 85, 86)
	CD24 and **CD44/Src/Integrin-β1** *FAK, paxillin*	Promote	U251, H1299, H23, H460, A569, SHP-77, AZ521, HT-29, MTLy, RKO, HCT-116	mβCD, Filipin, Simvastatin	(80–82, 84)
	CD44 *Ezrin*	Inhibit	MCF10a, MDA-MB-231		(87)
	SFK	Promote	MCF7, MDA-MB-231	LRT-SIFP (inhibits the SFK activity in LRs)	(83)
	Integrin-α5β1/LFA-1/β3	Promote	Jurkat, F111, P-815	mβCD, mal-βCD (inhibitor)	(70, 72, 73)
Necrosis	**MLKL** *TNFa/RIPK1/RIPK3*	Promote	HEK293T, L929, Jurkat, HeLa, CHO, SKOV3, TOV112D, A2780, A2780CP, PE01, PE04		(95–97)
Anoikis	**Integrin/FAK** *Bcl-xL, Akt, Src*	Inhibit	A431, PZ-HPV7, MCF10A, MCF7, MDA-MB-231, PC-3, LNCaP	Simvastatin, mβCD	(113, 114)
	HIF1α *EGFR/Akt/mTOR*	Inhibit	A431, HeLa	mβCD	(115)
Apoptosis	**DR4/DR5**	Promote	HT29, HCT116, SW480, SW620, H460, A549, A549, H1792, H596, CEM, HD-MyZ, I-83, JMV-3, NALM-6, BJAB	Nystatin	(102–106)
	Fas/CD95, *FADD, procaspase-8/10, JNK, Bid, Caspase-3*	Promote	HL-60, Jurkat, MM1S, MM144, U266	mβCD, filipin	(100, 101)
	Akt	Inhibit	NIH3T3	mβCD	(110)

Note: Proteins in lipid rafts are bolded and associated pathways/proteins are italicized.

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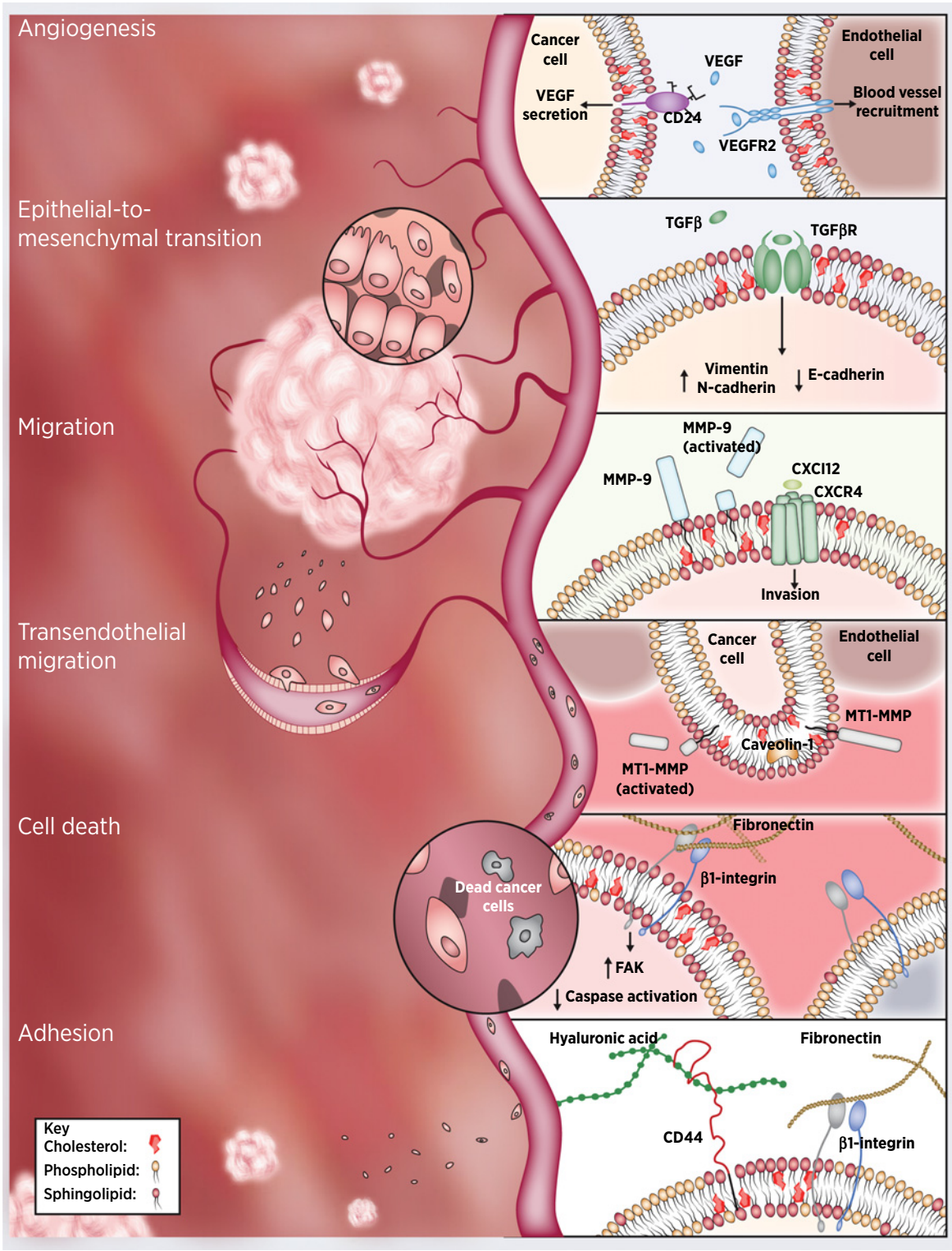

Figure 1.

Lipid rafts play an important role in cancer cell metastasis and cell death. Angiogenesis: CD24 raft colocalization promotes VEGF secretion of cancer cells, while VEGFR2 raft colocalization enhances angiogenesis upon VEGF activation (24, 27). EMT: TGFβ receptor is reliant on localization with rafts to promote downstream EMT signaling pathways (32). Migration: Raft colocalization promotes MMP-9 activation and CXCR4-mediated cell migration (31, 44). TEM: Lipid rafts are enriched at invadopodia where caveolin-1 colocalizes with MT1-MMP to promote TEM (64, 65). Cell death: Integrin–ECM detachment leads to FAK deactivation and the anoikis response (112). Adhesion: colocalization of CD44 and β1 integrin enhance matrix-dependent cell adhesion to hyaluronic acid and fibronectin, respectively (20, 82).

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adhesions and cancer cell migration (39). For example, disrupting lipid rafts in human melanoma decreased migration velocity and inhibited lamellipodia formation by inducing the formation of actin stress fibers, preventing the disassembly of focal adhesions (40). One interesting study designed a ruthenium complex–based peptidic molecule that self-assembles into nanofibrils on lipid rafts (41). The nanofibrils cross-linked lipid rafts, causing them to aggregate into large chained structures. This raft constriction caused focal adhesion suppression and decreased cell migration. Another study found that the potassium channel, SK3, associates with calcium channel, Orai1, in lipid rafts to upregulate calcium influx and promote cell migration and bone metastasis (42). Treating with the alkyl-lipid, ohmline, translocated the SK3–Orai1 complex out of lipid rafts, impairing calcium entry and attenuating cell migration.

Matrix metallopeptidase proteins (MMP) play a critical role in extracellular matrix (ECM) degradation during cancer cell migration (43). One study found that enhanced MMP-9 localization into lipid rafts augmented cell migration and metastatic potential in mouse Lewis lung cancer (44). Disrupting rafts with mβCD significantly decreased MMP-9 secretion and suppressed invasiveness of these highly metastatic cells. Similarly, another study found that mβCD treatment reduced colocalization of the GPI-anchored membrane protein, uPAR, and MMP-9 in lipid rafts, decreasing migration of breast cancer cells (21). MMP-1 is also important in promoting cancer cell migration. A study found that squalene synthase was upregulated in metastatic lung cancers and caused lipid raft enrichment of TNF receptor-1 (TNFR1), enhancing NF-κB activation and leading to MMP-1 upregulation (45). Treatment with mβCD inhibited TNFR1–lipid raft colocalization, abrogating promigratory signaling and reducing the metastatic potential of lung cancer cells.

Lipid rafts also influence chemotactic signaling of directed cell migration. The CXCL12/CXCR4 chemokine axis has been extensively studied for its role in driving cancer cell migration (46, 47). In metastatic prostate cancer, this signaling axis was found to transactivate EGFR, HER2, and Src selectively within lipid raft microdomains (48). CXCR4 has been shown to colocalize with phosphatidylinositol 4-kinase IIIα (PI4KIIIα) within lipid rafts to promote CXCL12-stimulated cell invasion (49). Likewise, CXCL12-induced c-MET activation and cell migration were found to be dependent on lipid raft protein, caveolin-1, and inhibition of rafts with nystatin decreased activation of the CXCL12/CXCR4 axis (31). Lipid rafts are also essential for androgen receptor- and EGFR-mediated cell migration (50). EGFR was found to colocalize into lipid rafts, while mβCD raft disruption inhibited EGF-induced chemotaxis and actin polymerization in breast cancer cells. In prostate cancer cells, low testosterone caused accumulation of transient receptor potential melastatin 8 (TRPM8) with androgen receptors in lipid rafts, thereby inhibiting TRPM8 and promoting cell migration (51).

Flotillin and caveolin are also implicated in driving cell migration. By reducing levels of flotillin-2 in breast cancer cells, tumor volume, metastatic capability, and proliferation decreased by inhibiting PI3K/Akt signaling (52, 53). In addition, CD133, an oncogenic cancer stem cell (CSC) marker, has been shown to colocalize with caveolin-1 in lipid rafts to increase invasiveness and chemoresistance in pancreatic tumor–initiating cells (54).

TEM

Metastatic dissemination relies on the cell's ability to enter into (intravasation) and exit from (extravasation) the vasculature via TEM (55). The MUC1/intercellular adhesion molecule-1 (ICAM1) interaction activates a cascade through which physical barriers for TEM are abrogated (56). MUC1 proteins, found to be concentrated in lipid rafts, bind to ICAM1 on endothelial cells to facilitate TEM (57). In pancreatic cancer cells, one study found that IGF1 induces CD44/C1QBP complex formation in lipid rafts, activating PI3K/MAPK signaling pathways and promoting TEM. Knockdown of C1QBP inhibited complex formation in rafts, decreasing TEM (58).

Multiple studies have established that invadopodia formation is required for successful intravasation and extravasation (59, 60). For example, one study found that invadopodia formation through N-WASP–mediated actin cytoskeleton reorganization is required for cancer cell intravasation (61). Another study found that cells extend invadopodia through the endothelium prior to extravasation; by inhibiting invadopodia formation, extravasation and metastatic tumor formations were decreased (62). There is strong evidence that invadopodia formation in cancer cells relies on lipid raft enrichment. Proteases, FAPα and MT1-MMP, were found to colocalize with caveolin-1 in lipid rafts, recruiting invadopodia in cancer-associated fibroblasts (CAF) and breast cancer cells, respectively (63, 64). Disruption of lipid rafts via mβCD and *CAV1* gene silencing impeded MT1-MMP activation and suppressed invadopodia formation (64). Similarly, another study found that caveolin-1 activates MT1-MMP in invadopodia through the PI3K/Akt/mTOR pathway under low shear stress (65). Treatment with mβCD inhibited MT1-MMP expression and prevented invadopodia formation, while *CAV1* silencing curbed metastatic formation in animal models. An additional study revealed that podoplanin is recruited into invadopodia via lipid rafts and is essential for invadopodia stability by controlling the ROCK–LIMK–Cofilin pathway (66). Taken together, these studies show that lipid rafts are important facilitators of TEM mechanisms and raft perturbation may be a viable therapeutic strategy to curb intravasation and extravasation.

Cancer cell adhesion

The likelihood of cancer cells surviving the disadvantageous stresses within the metastatic cascade is contingent upon their interactions with the ECM, fibroblasts, bloodborne cells, and the endothelium (67). Cholesterol and sphingolipids, two integral components of lipid rafts, are necessary for the ECM adhesion of cancer cells (68, 69). Elevated cholesterol induces redistribution of integrins, resulting in increased cell attachment to fibronectin (70). Conversely, membrane sphingolipid depletion prevents binding to fibronectin (71). One study found that while lipid raft levels did not contribute to *de novo* synthesis of integrin, the depletion of lipid rafts with 6-O-α-maltosyl-β-cyclodextrin (malβCD) demonstrated that lipid raft levels were directly correlated with integrin activation and fibronectin adhesion (72). A different study obtained similar results with human T cells. In both primary human T cells and Jurkat lymphoma cells, mβCD-induced raft depletion resulted in decreased integrin-α5β1 and -αLβ2 (LFA-1)-mediated adhesion (73). These studies reinforce the role that lipid rafts play in contributing to integrin-mediated ECM adhesion.

CD44 has been implicated in cancer progression and metastasis as a dynamic regulator of cell migration and adhesion, and its roles include initiating circulating tumor cell (CTC) adhesion and rolling on the endothelium (74–76). Similarly, integrins, particularly integrins of the β1 subtype, are critical for cancer cell adhesion and vasculature survival in transit (77–79). The translocation of integrins and adhesion-related cluster of differentiation molecules to lipid rafts is critical for adhesion-related maintenance of cell migration. One study found that raft disruption of TNBC cells via mβCD treatment significantly decreased cell adhesion on fibronectin- and vitronectin-coated substrates (20). Likewise, cholesterol depletion caused CD44 shedding

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from lipid rafts in cancer cells, suppressing adhesion, migration, and endothelial cell rolling (80, 81). CD44 is known to interact with C1QBP in rafts to activate PI3K/MAPK downstream, a signaling pathway that also promotes cell adhesion and other prometastatic phenotypes (58). In addition, CD44 clustering in lipid rafts was found to activate Src family kinases (SFK), enriching β1 integrins into lipid rafts to promote cell adherence and matrix-derived survival (82). By inhibiting SFK activity in lipid rafts, cancer cell adhesion of breast cancer cells was inhibited (83). Similarly, CD24 was found to interact with, and promote c-Src translocation into lipid rafts, enhancing formation of focal adhesions, integrin-mediated adhesion, and cell spreading (84). Using mβCD, emodin, and gambogic acid, studies have shown that blocking focal adhesion complex protein localization into lipid rafts inhibits tumor cell adhesion (85, 86).

While many studies support the promigratory role of lipid raft–colocalized CD44, its role remains controversial. For example, one study demonstrated that enhanced palmitoylation of CD44 drives colocalization with rafts, limiting associations with its cytoskeletal linker binding partner, ezrin, to suppress migration in invasive breast cancer subtypes (87). Indeed, raft affinity of CD44 is largely regulated by one of two mechanisms: palmitoylation, which enhances affinity and reduces binding to cytoskeletal linkers, and phosphatidylinositol 4,5-bisphosphate (PIP2) membrane concentration, which decreases raft affinity, thereby accelerating formation of the CD44–adaptor complex (88). This confounding role of CD44 may be explained by the dynamic nature of protein–raft colocalization, that is, while palmitoylated CD44 may exist within rafts in an "inactive" state, rapid depalmitoylation may induce raft dissociation and subsequently promote cell adhesion. Meanwhile, CD44 shredding from rafts as a result of cholesterol depletion prevents the possibility of CD44 dissociation to "nonraft" PIP2 localized regions, thereby abrogating CD44-mediated cell adherence.

Lipid Rafts and Cell Death

Cell death is a vital function that occurs naturally in the body, one that mediates the removal of damaged or infected cells and maintains tissue homeostasis (89). Mechanisms of cell death are especially important in the body's response to cancer; most cells that develop DNA abnormalities and cell checkpoint mutations undergo programmed cell death before they can proliferate further (90). Immunity to this process is one of the hallmarks of cancer, resulting in uncontrollable division and metastasis (91). The roles of lipid rafts in various types of cell death, including necrosis, apoptosis, and anoikis, have been studied extensively in recent years (**Table 1A**).

Necrosis

Necrosis is a form of unprogrammed cell death that occurs in response to trauma and other stress-inducing stimuli, resulting in an inflammatory cell death response (92). More recently, it has been suggested that necrotic cell death proceeds in a programmed manner similar to apoptosis (93). This pathway, termed "necroptosis," acts through a caspase-independent signaling cascade. Several studies have evaluated the role of lipid rafts in this necroptotic pathway.

Mixed lineage kinase domain-like pseudokinase (MLKL) has been identified as a downstream protein in the TNFα-induced necroptosis signaling cascade (94). One study demonstrated that oligomerization of MLKL proteins and translocation into lipid rafts are necessary for necroptosis in murine fibrosarcoma cells (95). Translocation of the oligomerized MLKL complex into lipid rafts supported sodium influx, increased osmotic pressure, and cell rupture. Similarly, another study demonstrated MLKL-induced membrane permeabilization of PIP-containing liposomes (96). Through selective mutation, it was discovered that binding of positive amino acids on the oligomerized MLKL complex to PIPs allows for recruitment to lipid rafts. Inhibiting PI5P and PIP2 led to decreased necroptosis in Jurkat and murine fibrosarcoma cells. A subsequent study evaluated the effect of ceramide nanoliposomes (CNL) on MLKL expression, demonstrating that CNLs strongly promoted MLKL activation–driven necroptosis, but not apoptosis in ovarian cancer cells (97). These results suggest that CNLs form lipid raft mimetics, which promote MLKL translocation and necroptosis, supporting the role of lipid rafts in necroptosis. Given that many cancer cells display resistance to apoptosis, therapeutic targeting and activation of the necroptotic pathway present an exploitable alternative to induce cell death.

Apoptosis

Apoptosis, is a noninflammatory, programmed cell death pathway (89, 98). External activation of death receptor in the TNF superfamily results in the recruitment of the death-inducing signaling complex, caspase activation, DNA fragmentation, and cell death (99). The majority of lipid raft–apoptosis synergism studies are in relation to the colocalization of CD95 (Fas) and death receptors 4/5 into rafts, forming clusters of apoptotic signaling molecule-enriched rafts to enhance apoptotic signaling (100–105). Chemotherapeutic agents, such as perifosine, and lipid raft agonists, such as resveratrol, have been shown to promote death receptor translocation into rafts, warranting further investigation into combination treatments of chemotherapeutic raft synergism with death-inducing ligands (101, 106, 107). For additional information, studies of raft-mediated death ligand signaling have been extensively covered in recent reviews (16, 108, 109).

Apart from death receptor signaling, some studies have conversely implicated rafts as being prosurvival, apoptotic regulators. For example, one study demonstrated that mβCD-induced raft disruption resulted in G_2–M-phase arrest and eventual apoptosis in breast cancer cells (20). Likewise, protein kinase B (Akt), an important prosurvival protein, was shown to localize into lipid rafts (110). Lipid raft disruption using mβCD led to a decrease of Akt activity and increased apoptosis in mouse fibroblast cells.

Anoikis

Anoikis is a specialized type of apoptosis that is activated upon cell detachment, and developed resistance to anoikis is an essential step in cancer metastasis (111, 112). The loss of integrin attachment to matrix results in an inactivation of apoptosis inhibitor, FAK, leading to caspase activation. Because lipid rafts facilitate integrin interactions and cell adhesion, depletion of lipid rafts has also been shown to directly result in anoikis-like death. When treated with cholesterol-inhibiting agents, human breast, prostate, and epidermoid carcinoma cells showed decreased lipid raft formation, Bcl-2 downregulation, caspase-3 activation, and Akt downregulation, inducing anoikis-like apoptosis (113). Similarly, another study demonstrated that simvastatin-induced cholesterol depletion resulted in raft internalization and FAK downregulation, resulting in cell detachment, caspase-3 activation, and anoikis (114).

The lipid raft association of hypoxia inducible factor 1 (HIF1) in cell attachment has also been studied. HIF1α is produced under hypoxic conditions and promotes cell survival. Interestingly, hypoxic conditions have been shown to correlate with decreased lipid rafts, suggesting that HIF1α influences lipid raft production. Epidermoid carcinoma cells treated with mβCD under normoxic conditions demonstrated

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upregulated HIF1α, suggesting that the cells underwent HIF1α-mediated lipid raft production in response to cholesterol depletion (115). Silencing of HIF1α led to accelerated cell detachment and anoikis. These studies demonstrate the complexities of lipid raft involvement in mechanisms of cell death. Exploiting anoikis-like apoptosis mechanisms through lipid raft augmentation may be a viable method to prevent cancer cell survival upon detachment.

Lipid Raft–Associated Biomarkers of Cancer Progression and Metastasis

Apart from their roles in cancer metastasis and cell death, components of lipid rafts, namely caveolin and flotillin, have received much attention as clinical biomarkers. There are confounding oncogenic and tumor-suppressing roles of these protein families surrounding different aspects of tumor growth and metastasis observed clinically. This section aims to elucidate the seemingly contradictory roles of caveolins and flotillins in metastatic progression and patient prognosis for a range of cancers. The prognostic roles of these proteins are summarized in **Table 1B**.

Flotillins

Flotillin-1 and flotillin-2 are widely believed to be metastatic drivers in a variety of tumors (116). Two recent meta-analyses found that flotillin overexpression predicts poor overall survival, lymph node metastasis, and distant metastasis in a multitude of solid tumors (117, 118). In breast cancer, flotillin-2 mRNA and protein overexpression were indicative of poor prognosis in both early- and late-stage disease (119). Meanwhile, increased flotillin-1/flotillin-2 expression correlated with poor survival and enhanced pelvic, inguinal, and femoral lymph node metastasis in both cervical and vulvar squamous cell carcinoma (120–122). High flotillin-1 and flotillin-2 levels were indicators of aggressive characteristics and poor prognosis of hepatocellular carcinoma and intrahepatic cholangiocarcinoma, respectively (123, 124). In both left and right colorectal cancer, flotillin-1 was overexpressed in cancerous tissue and was associated with tumor volume, differentiation, and proliferation, while flotillin-2 levels were associated with lymph node and distant metastasis (125, 126). Moreover, flotillin-1 and flotillin-2 were found to promote metastasis via TGFβ-mediated EMT induction in patients with small-cell lung cancer and nasopharyngeal carcinoma, respectively (127–129).

While mounting evidence implicates flotillin overexpression with tumor progression and metastasis, one study revealed that low expression of flotillin-1 correlates with poor prognosis in patients with neuroblastoma (130). Flotillin-1 regulated neuroblastoma progression by facilitating binding, endocytosis, and degradation of membrane-localizing anaplastic lymphoma kinase (ALK). Thus, it is possible that this conflicting, antimetastatic role of flotillin-1 may be constrained to subsets of cancers that possess high levels of oncogenic ALK mutants, for example, NSCLC and neuroblastoma (131).

Caveolins

While the oncogenic roles of flotillin-1 and -2 in the clinic are generally agreed upon, there remains contradictory evidence for the clinical role of caveolins, particularly caveolin-1. For example, multiple studies in bladder cancer have demonstrated high caveolin-1 expression is associated with cancer progression, high-grade tumors, and poor patient prognosis (132, 133). Conversely, high stromal caveolin-1 in early prostate cancer was found to correlate with decreased malignancy, longer survival, and favorable prognosis when managed by watchful waiting (134). In gastric cancers, after tumor resection, high caveolin-1 expression correlated with tumor relapse and lymph node metastasis (135, 136). However, in colorectal cancer–derived liver metastasis after hepatectomy, weak stromal caveolin-1 expression was a predictor of poor prognosis (137). Furthermore, enhanced tumoral caveolin-1 correlated with gemcitabine drug resistance and advanced pathologic stage and metastasis in patients with NSCLC (138, 139). Taken together, these studies indicate tumoral caveolin-1 is an indicator of poor prognosis, while stromal caveolin-1 is favorable. While this is true for many studies, in thyroid cancer, expression of stromal caveolin was found to be upregulated in more aggressive carcinoma subtypes (140).

Breast cancer may be the most confounding cancer type when it comes to the clinical relevance of caveolin-1 (141). Overexpression of caveolin-1 in CAFs correlated with increased low histologic grade and favorable prognosis, while absent or depleted stromal caveolin-1 increased the risk of recurrence and predicted lymph node metastasis in early ductal carcinoma *in situ* (DCIS; refs. 142, 143). In addition, high levels of epithelial caveolin-1 were correlated with more aggressive, TNBC subtypes (144). These findings are supported by a study that examined subgroups of patients with breast cancer with high tumoral caveolin-1 (T++) and weak stromal expression (S−). T(++)/S(−) subgroups showed exceptionally poor clinical outcomes compared with T(++) and S(−) groups taken individually (145). This is consistent with the differential roles of epithelial and stromal caveolin-1 in cancer prognosis discussed above. However, this may not always be the case. One study of metastatic breast cancer found caveolin-1 expression was decreased in brain metastases compared with primary DCIS (146). Furthermore, another study demonstrated that depletion of caveolin-1 in lipid rafts of breast tumors promoted cellular autophagy–mediated cell survival under starvation conditions (147). This supports the multifaceted functionality of caveolins within breast cancer metastasis, warranting further investigation before implementation as a clinical biomarker.

Conclusions and Future Perspectives

Within the past few decades, numerous studies have implicated lipid rafts as drivers of oncogenic and prometastatic processes. However, the role of rafts in specific areas of metastasis has remained elusive. For example, little is known about how lipid rafts affect CTC survival in the vasculature. While we have presented studies that demonstrate that rafts are vital for anoikis resistance, endothelial cell rolling, and vasculature-related adhesion mechanisms, evidence of this in spontaneous CTCs in animal models remains nonexistent. This is likely a consequence of the aforementioned inadequacies of *in vivo* and real-time lipid raft detection methods. Moreover, no known study has examined the presence or effect of lipid rafts in primary CTCs isolated from human patients. Given the heterogeneous landscape of CTCs, elucidating the undiscovered roles of rafts and raft-associated proteins may be instrumental in predicting CTC subpopulations that will survive in transit and proceed to colonize secondary tumors (148).

Studies have shown that excessive cholesterol in cancer cells is a biomarker of chemoresistance and stemness, but the role of raft microdomains in CSCs remains largely unknown (149). CD44 remains a prominent CSC marker in a variety of cancers, and we have discussed a multitude of studies demonstrating the propensity of CD44 to coalesce into raft fragments. However, other prominent CSC surface markers, such as CD133, remain understudied despite recent methodologies for isolating $CD133^+$ raft fractions (150). It was recently demonstrated that CD133 localizes into lipid rafts in pancreatic cells to

Table 1B. The role of flotillin and caveolin families of proteins in metastatic progression and patient prognosis.

Protein family	Cancer type	Summary	Protein	Prognosis	References
Flotillin	Breast cancer	↑ flotillin-2 is significantly correlated with clinical stage, metastasis, and shorter overall survival	Flotillin-2	Poor	(119)
	Cervical cancer	↑ flotillin-1 and flotillin-2 corelates with pelvic lymph node metastasis, clinical stage, tumor differentiation, and poor overall survival	Flotillin-1 and -2	Poor	(120, 121)
	Colorectal cancer	↑ flotillin-1 and flotillin-2 are associated with tumor volume, depth of invasion, lymph node metastasis, distant metastasis, increased proliferation, and poor survival	Flotillin-1 and -2	Poor	(125, 126)
	Liver (hepatocellular and intrahepatic cholangio carcinoma)	↑ flotillin-1 and flotillin-2 in cancerous tissue and positively correlated with tumor size, clinical stage, vascular invasion, lymph node metastasis, and relapse.	Flotillin-1 and -2	Poor	(123, 124)
	Nasopharyngeal carcinoma	↑ flotillin-2 promotes tumor progression and is positively associated with a metastatic phenotype and sorter overall survival	Flotillin-2	Poor	(128, 129)
	Neuroblastoma	↓ flotillin-1 correlated with poor prognosis and mRNA expression inversely correlate with clinical malignancy grade	Flotillin-1	Favorable	(130)
	Small-cell lung cancer	↑ flotillin-1 is highly expressed in small-cell lung cancer and strongly correlates with clinical stage, distant metastasis, and poor survival	Flotillin-1	Poor	(127)
	Various	↑ flotillin-1 and flotillin-2 are associated with shorter overall survival, decreased disease-free survival, and increased lymph node metastasis	Flotillin-1 and -2	Poor	(117, 118)
	Vulvar squamous cell carcinoma	↑ flotillin-1 predicts poor overall and progressive free survival and is an oncogenic facilitator of inguinal/femoral lymph node metastasis	Flotillin-1	Poor	(122)
Caveolin	Bladder cancer	↑ caveolin-1 in cancerous tissues and high-grade tumors	Caveolin-1	Poor	(132, 133)
	Breast cancer	↑ stromal caveolin-1 in CAFs correlated with increased 5-year survival, low histologic grade while absence or ↓ stromal caveolin-1 increased risk of recurrence and predicted lymph node metastasis	Caveolin-1 (stromal and epithelial)	Favorable (stromal)	(142–145)
		↑ epithelial caveolin-1 correlates with high histologic grade, lack of hormone receptors, and decreased survival		Poor (tumoral)	
		Tumor + stromal cancer subtypes had poor survival			
	Breast cancer (brain metastases)	↑ caveolin-1 negatively regulates Stat3, inhibiting brain metastasis from breast cancer	Caveolin-1	Favorable	(146)
	Colorectal cancer (liver metastases)	↓ stromal caveolin-1 is associated with decreased disease-free and overall survival after hepatectomy	Caveolin-1 (stromal)	Favorable	(137)
	Gastric cancer	↑ caveolin-1 strong indicator of poor median overall survival, tumor grade, lymph node involvement, and decreased relapse-free survival in resected gastric cancer	Caveolin-1	Poor	(135, 136)
	NSCLC	↑ caveolin-1 expression correlated with pathologic stage, chemoresistance, and decreased overall and disease-free survival	Caveolin-1	Poor	(138, 139)
	Prostate cancer	↑ stromal caveolin-1 associated with favorable prognosis, longer survival while expression decreased in malignant tissues and higher tumor stages	Caveolin-1 (stromal)	Favorable	(134)
	Thyroid cancer	↑ stromal caveolin-1, caveolin-2, and caveolin-3 in anaplastic carcinoma (poor prognosis) compared with papillary thyroid carcinoma and diffuse sclerosing variant of papillary carcinoma (more favorable prognosis)	Caveolin-1, -2, and -3 (stromal)	Poor	(140)

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enhance chemoresistance, further motivating investigation into other CSC-related proteins (54). Lipid rafts may be a vital missing link needed to fully understand the formation of CSC phenotypes, while also shedding light into mechanisms of senesce and therapeutic resistance. Furthermore, abrogating the juxtaposition of lipid rafts and stemness-related proteins via raft antagonization may provide a means of reverting CSCs into more druggable cellular phenotypes.

While there has been substantial research done on the contribution of lipid rafts in apoptotic and anoikis pathways, the role of lipid rafts in necroptotic pathways has not been studied sufficiently. This review has discussed the importance of lipid rafts in the MLKL-mediated necroptotic pathway, in response to TNF superfamily ligands. However, it is important to note that necroptosis can also be induced by double-stranded RNA and lipopolysaccharides, through TLR 3 and 4 (151, 152). Necroptosis can also be initiated through IFNs (153). It is currently unknown how and whether lipid rafts play a role in this pathway, perhaps in an MLKL-independent fashion. Leveraging known mechanisms of raft-associated apoptosis may be key for therapeutic exploitation. For example, it was mentioned that many chemotherapeutic agents have been shown to translocate death receptors into lipid rafts to enhance apoptotic signaling upon ligand activation. Clinical evaluation of combination treatments of chemotherapeutics and death-inducing ligands (TRAIL and Fas) may prove effective to overcome mechanisms of therapeutic resistance.

Moving forward, a major challenge will be developing targeted therapeutics and drug delivery strategies to selectively disrupt rafts that facilitate oncogenic and prometastatic processes. While FDA-approved cholesterol lowering drugs exist, they tend to be nonspecific and are not yet approved for cancer therapy (154). In addition, the off-target and downstream signaling implications following statin-mediated cholesterol depletion in cancer have yet to be fully elucidated. Given these translational challenges, we expect not only forthcoming research on raft antagonizing compounds, but raft-targeted delivery modalities as well. For example, one group designed mβCD–hyaluronic acid–ceramide nanoassemblies that selectively target and disrupt CD44-positive lipid rafts (155). Engineering novel drug delivery modalities for raft targeting and regulation will be critical for the development of antimetastatic cancer therapies.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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