Minireview *Highlight article*

The role of cholesterol and cholesterol-driven membrane raft domains in prostate cancer

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Impact statement

Prostate cancer remains the most common malignancy and second most frequent cause of cancer-related death in men. Cholesterol levels are usually higher in prostate cancer cells. This affects the cell membrane composition, with cholesterol and sphingolipid-containing raft membrane domains becoming a greater component. In addition to polar lipids, these domains recruit and regulate certain types of protein, including various cell signaling proteins that are critical to cancer cell survival and invasiveness. This suggests that membrane rafts have a regulatory role in tumor progression, making them a potential target in prostate cancer treatment.

Abstract

Membrane rafts are heterogeneous and dynamic domains that are characterized by tight packing of lipids. They are enriched in cholesterol, sphingolipids, and certain types of proteins. Among these are various cell signaling proteins, which indicate that rafts play an important role in cell signal transduction pathways, including some involved in cancer development, progression, and invasiveness. Due to their increased cholesterol content, raft domains exhibit lower fluidity than the surrounding membrane. The cell membranes of some solid tumors, such as breast and prostate cancer, contain higher levels of cholesterol, which means larger raft domain can form in those membranes. This may stimulate signaling pathways to promote tumor growth and progression. This review focuses on the known raft-dependent regulatory mechanisms that promote prostate cancer progression.

Keywords: Cholesterol, membrane raft domains, caveolae, signaling pathways, prostate cancer

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Introduction

Prostate cancer remains the most frequently detected malignancy and the second most frequent cause of cancer-related death in men. An emerging area of research indicates that membrane rafts play a role in neoplastic or tumor cell growth and invasiveness. Two factors have brought particular attention to membrane rafts as possible pharmacological targets in the treatment of these tumors.

First, caveolin-1 was first identified as a prognostic marker for prostate cancer in 1998, indicating that the caveolae subclass of membrane raft domains may have a role to this malignancy.[1] Caveolins localize almost exclusively to this subclass of membrane raft domains, where they act as structural organizers and are thus responsible for their characteristic invaginated morphology.[2] In this way, caveolin-1, a marker for membrane raft domains, is also considered a prominent marker of prostate cancer progression.[3,4]

Second, the cells of prostate cancer tumors are known to *de novo* synthesize high quantities of fatty acids and cholesterol independent of circulating lipid levels.[5] Cholesterol accumulates in membrane domains and stabilizes them by interacting with other lipids and a certain class of raft proteins to form liquid-ordered domains. The two main types are caveolar and planar membrane rafts.[6] Both types of raft recruit receptors and their downstream targets and regulate numerous cellular signaling pathways related to cell growth, cycle progression, adhesion, migration, and apoptosis. These processes all play major roles in the initiation and development of many types of tumor.[7] Cholesterol-depletion experiments have deepened the understanding of the effect of membrane raft disorganization on cellular activity. In prostate cancer xenografts specifically, an elevated level of blood cholesterol has been shown to increase membrane raft content, promote tumor growth, and reduce apoptosis.[8] Therefore, studies on the

role of cholesterol and cholesterol-dependent membrane raft domains point attention of researchers working on prostate cancer progression and therapy.

Aberrant regulation of cholesterol metabolism and prostate cancer progression

The cholesterol content of cell membranes is well known to be tightly regulated in normal cells. Dysregulation mechanisms in the control of its content are frequently found in various neoplastic cell types. Such dysregulated control has been implicated in the development of aggressive or advanced prostate cancer.[9] Diverse mechanisms have been suggested to underlie cholesterol enrichment and its role in promoting prostate cancer development (summarized in Table 1), including: alterations in the enzymes of cholesterol metabolism, particularly 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase,[10] enhanced uptake from the bloodstream,[16] impaired regulation of low-density lipoprotein (LDL) receptors,[11] and dysregulated cholesterol discharge in the cells via the ATP-binding cassette A1 transporter (ABCA1).[12]

One of the biological roles of cholesterol is to be a precursor molecule from which steroid hormone synthesis begins. This includes the synthesis of androgenic hormones. It was recently pointed out that prostate cancer cells employ a mechanism of *de novo* androgen synthesis from the increased level of cholesterol.[13,17] It was also found that in these cells, androgens affect lipid biosynthesis directly by enhancing the transcription of two key genes: the fatty acid synthase and HMG-CoA reductase[18] and farnesyl pyrophosphate synthase. Androgens were also suggested to be responsible for the accumulation of cholesterol and other lipids in the prostate cells.[19]

Multiple studies have shown a relationship between high cholesterol levels and a higher risk of prostate cancer development and progression.[20–23] Elevated cholesterol may contribute to these processes on many levels. One study found that the proliferation of PC-3 and LNCaP prostate carcinoma cells was suppressed by the statin-mediated inhibition of HMG-CoA reductase activity, which led to a reduction in cellular concentrations of mevalonate, a precursor molecule formed from conversion of HMG-CoA during cholesterol biosynthesis. This inhibition correlated with the G1 phase cell cycle arrest.[24]

In PC-3 cells, atorvastatin was shown to induce autophagy by inhibiting synthesis of geranylgeranyl derivatives. This was evidenced by the increased levels of LC3-II (microtubule-associated protein 1A/1B-light chain 3 conjugated to phosphatidylethanolamine), which is an essential component for the assembly of autophagosomes.[25]

Control of cholesterol homeostasis in prostate cancer cells largely involves the uptake of cholesterol esters and cholesterol-containing LDLs through the LDL receptor (LDLR). This constitutes the LDLR pathway, which supplies cells with essential polyunsaturated fatty acids used for the synthesis of eicosanoids such as prostaglandin E2. Elevated prostaglandin levels have been observed in malignant human prostate cells[26] and in carcinogen-induced rat prostate cancer cells.[27] Increased synthesis of prostaglandins influences prostate cancer development and growth by activating cell proliferation and through the carcinogenic impact of fats and hormones on the gland. The mechanism involving increased production of the LDLR by prostate cancer cells seems to be connected with increased eicosanoid synthesis and cell growth stimulation.[11]

It was recently reported that apolipoprotein E (ApoE) controls dendritic cell function by promoting cholesterol and lipid transfer from cells to HDL.[28] Membrane raft enrichment as a result of ApoE loss causes compartmentalization on the cell surface, predominantly of the MHC-II molecule, inducing T-cell activation. The reestablishment of cholesterol homeostasis through application of the wild-type ApoE3 isoform to the cells restores the initial phenotype of activated dendritic cells, which was induced by a decrease in the content of membrane raft domain and in the level of raft-associated MHC-II. This shows that ApoE has a physiological role in cholesterol-mediated adaptive immune responses.[28]

Sterol regulatory element-binding protein 1 (SREBP-1), a potent transcription regulator of genes engaged in fatty acid biosynthesis, is controlled by the mammalian target

Table 1. Molecular mechanisms accounting for cholesterol enrichment and its role in promoting prostate cancer development and progression.

Molecular mechanisms controlling cholesterol level	Impact on prostate cancer pathways and progression
Increased expression level of sterol response element-binding protein-1 and -2 (SREBP-1a, -1c, and -2)[10]	Alteration in the enzymes of cholesterol metabolism: HMG-CoA reductase and farnesyl pyrophosphate synthase
Loss of feedback regulation of low-density lipoprotein (LDL) receptors[11]	Overproduction of LDLR as an important mechanism in cancer cells leading to the synthesis of more essential fatty acids and prostaglandins, which stimulate cell growth
ABCA1 promoter hypermethylation and loss of protein expression[12]	Dysregulated cholesterol efflux via the ATP-binding cassette A1 transporter (ABCA1)
• *De novo* cholesterol synthesis (via squalene monooxygenase; SQLE) • *De novo* steroidogenesis via CYP17A[13]	Synthesis of androgens from elevated cholesterol to activate the AR
Direct modification of the N-terminal signaling domain of the Hedgehog (Hh) proteins[14,15]	Maturation and signal transduction of the Hh pathway essential in cell pluripotency and cancer aggressiveness
Cholesterol accumulation in lipid rafts[8]	• Overactivation of pro-proliferative and growth pathways, such as PI3K/AKT and EGFR • Downregulation of apoptotic pathways

AR: Androgen Receptor; EGFR: Epidermal Growth Factor Receptor; LDLR: LDL Receptor.

of rapamycin (mTOR) complex 1. Its activation leads to upregulation of the PI3-kinase/AKT (Protein Kinase B) signaling pathway and hence to cell growth.[29,30] Experimental data show that cholesteryl esters accumulate in advanced prostate cancer cells due to loss of the tumor suppressor gene *PTEN*. This leads to upregulation of the PI3K/AKT/mTOR pathway, which in turn causes the activation of SREBP and LDLR.[31]

Prostate cells export cholesterol via ABCA1, the expression of which is significantly downregulated in androgen-independent LNCaP cells, suggesting a negative relationship between the expression levels of the *ABCA1* gene and the progression of prostate cancer.[32] Lee *et al.* showed that hypermethylation of the ABCA1 promoter and gene inactivation in LNCaP cells led to reduced levels of the ABCA1 transporter and accumulation of cholesterol in the cells. This alteration was found to be a characteristic feature of high-grade prostate cancer.[12]

Cholesterol is involved in the activation of Hedgehog (Hh) proteins through direct modification of their glycine residue at the C terminus of their newly formed N-terminal signaling domain. The cholesterol-modified proteins are further palmitoylated at the N-terminus, resulting in highly hydrophobic, high-activity proteins that are tightly associated to the cell membrane. Hh proteins activate the Hh pathway, which is implicated in prostate tumor development and progression in both standard and therapy-resistant states.[33,34]

The hypothesis that accumulated cholesterol might be involved in cell proliferation through cell cycle regulation is based on recent findings on nuclear localization and chromatin-associated cholesterol. It has been shown that the level of chromatin-associated cholesterol increases just before the initiation of S phase. The translocation of cholesterol into the nucleus is probably facilitated by the peripheral-type benzodiazepine receptor (PBR), which was previously reported to function as a regulator of cholesterol transport to the inner mitochondrial membrane, which is also a rate-determining step in steroid biosynthesis.[14] Immunohistochemical analysis showed a preferentially increased PBR level around the nuclear periphery of cancerous cells when compared to the level found in prostate cells collected from an unaffected site. In the nucleus of prostate cancer cells, the ratio of nuclear cholesterol to cyclin E, a regulator of cell cycle expression, was shown to be almost twice as high as in normal prostate cells. Therefore, increased cholesterol concentration in the cell nucleus could be a stimulus for cell division.[15]

Raft domains as an element of lateral membrane organization

Cholesterol is one of the major lipid components of the plasmalemma and the intracellular membranes. It affects the physiological features of the membrane by controlling membrane fluidity and regulating negative membrane curvature through interaction with phospholipid acyl chains. These interactions are essential for creating liquid-ordered membrane microdomains. Another essential interaction/factor is hydrogen bond formation between cholesterol and sphingomyelin.[35] Lateral interactions of cholesterol with relatively saturated lipid or glycosylated lipid species separate the membrane into two distinct liquid phases. The liquid-ordered (Lo) phase is characterized by decreased trans-gauche freedom. It consequently has greater order than the bulk phase and is considered to be the model for membrane rafts. The liquid-disordered phase is fluid, containing less cholesterol and mainly unsaturated lipids.[6,36] Researchers agree that unstable nanoscale assemblies within the membrane, primarily oligomeric protein–cholesterol–lipid complexes, associate into larger (Lo-like) functional nanodomains, also known as membrane rafts (resting-state flat rafts). They are ~20 nm in diameter, and are more stable, highly dynamic ($t_{1/2}$ ~1 s), and detergent-resistant domains.[37,38] Further clustering of resting-state rafts leads to the formation of large micrometer scale assemblies called raft platforms, e.g. immunological synapses.[39]

Proteomic analyses of membrane raft lipid composition have shown that in addition to the dominant presence of sphingolipids (mostly sphingomyelin), cholesterol, and glycolipids, they contain other phospholipids, including some species of phosphatidyl serine and phosphatidyl ethanolamine (PE) that mainly have fully saturated or monounsaturated acyl chains. Phosphatidylethanolamine glycerophospholipids and plasmalogens seem to be dominant.[40–43] Results from Langmuir monolayer studies indicate that 1-stearoyl-2-linoleoyl-sn-glycero-3-phosphatidyl-ethanolamine forms a complex with cholesterol similar to that between sphingomyelin and cholesterol, while dipalmitoyl-PE does not bind cholesterol.[44] In addition to the importance of the key lipid composition of membrane raft domains, protein–lipid interactions also play key roles in raft regulation. Proteins of the stomatin/prohibitin/flotillin/HflK family, such as the scaffold proteins flotillin-1 and -2, and stomatin or stomatin-like protein are characteristic "permanent" residents of membrane rafts. These proteins are associated with membrane rafts, probably through interaction with cholesterol or oligomerization.[45,46] They include various palmitoylated, doubly acylated, and transmembrane proteins that partition into lipid raft domains.[47] Other more or less permanent components of membrane rafts include GPI-anchored proteins and proteins of the signal transduction pathways, such as tyrosine kinases of the src family, Gα subunits of heterotrimeric G proteins, endothelial nitric oxide synthase, and Hh proteins. Many of these signal transduction pathway proteins are modified through palmitoylation and myristoilation or with cholesterol, which is thought to increase the affinity of these proteins to raft domains.[48]

Due to the presence of various proteins involved in signal transduction pathways, membrane raft domains are implied to be engaged in the regulation of many signaling pathways. The mechanism(s) by which the proteins partition into membrane rafts are thought to include preferred solubility in more ordered domains and/or chemical affinity for raft lipids, which would be a result of the presence of specific domains binding selected raft components, e.g. CRAC motifs being responsible for the cholesterol-binding properties of some of the proteins[49] or a protein motif recognizing sphingolipids or specific glycolipids such as ganglioside.[50]

As mentioned, signal transmission is among the important biological processes that involve membrane raft domains. Of particular interest to cancer studies, they transmit signals coming from growth factor receptors and are therefore related to cellular proliferation and motility control. It is essential to establish the roles of membrane rafts as signaling platforms in cancer development[7] and their possible application as targets in anticancer therapy.[51]

Involvement of membrane rafts in signaling pathways promoting prostate cancer

By taking part in the assembly and maintenance of the integrity of cell membranes and regulating membrane fluidity, cholesterol participates in transmembrane signaling, cell–cell adhesion, and cell adhesion to the extracellular matrix. Through its engagement in membrane raft integration, cholesterol stimulates pro-proliferative pathways, such as PI3K/AKT and EGFR.

The first reports that related membrane rafts to the growth of prostate tumor cells showed that the EGF receptor is phosphorylated and more active within membrane rafts. EGFR activation leads to activation of AKT, which promotes survival of prostate cancer cells. Treatment of such cells with statins, which are cholesterol-lowering agents, disrupts raft domain organization and interferes with EGFR signaling.[52] When mice with LNCaP cell-derived xenografts were fed a high cholesterol diet, a raft-dependent increase in AKT phosphorylation was shown. It promoted tumor growth and reduced apoptosis. Treatment of these animals with simvastatin disrupted the raft domains in prostate cancer cells, reduced phosphorylation of AKT, and induced apoptosis.[8] Depletion of cholesterol from membrane raft domains not only inhibited EGFR/AKT but also markedly altered the phosphorylation status of ERK and the mitochondrial apoptosis pathway, including activation of caspases.[53] These findings indicate the crucial role of membrane rafts in prostate cancer development and validate cholesterol-lowering drugs as an effective factor in prostate cancer treatment.

Additional studies on *in vivo* and *in vitro* models of prostate cancer indicated a liver X receptor (LXR) as a modulator of membrane raft signaling. Treatment of LNCaP cells and xenograft mice with the synthetic LXR agonist T0901317 caused cholesterol efflux through ABCG1 upregulation, downregulated phosphorylation raft-associated AKT, and finally induced apoptosis. Atomic force microscopy analysis of the topography of the inner surface of the plasma membrane of LNCaP cells treated with LXR agonist revealed a dispersion of membrane raft domains. Confocal microscopy also revealed changes in flotillin 2 staining compared to untreated cells. These results suggest structural changes in membrane raft domains.[54]

One of the signaling pathways frequently activated in prostate cancer is the Hh pathway.[34,55] The Hh receptor complex of patched (Ptc) and smoothened (Smo) is localized within caveolin-1-enriched microdomains, where Ptc specifically interacts with caveolin-1. The active form of sonic Hh (Shh), the most studied vertebrate homolog of Hh, results from autoproteolysis and simultaneous covalent modification of the N-terminal part of the protein with a cholesterol molecule. The latter modification is not a condition of Ptc-binding as bacterially expressed Shh-N fusion proteins still showed biological activity. Several lines of evidence show that Ptc interacts with caveolin-1, recruiting Smo to the receptor complex, which is therefore located within caveolin-enriched domains. Cholesterol depletion experiments showed decreased amounts of both Ptc and caveolin-1 in caveolae, which indicate that cholesterol is involved in recruiting both Ptc and caveolin-1 to membrane raft microdomains. These data indicate that caveolin-1 may be essential for recruitment of the Hh receptor complex to caveolin-enriched microdomains.[56]

Other signaling pathways related to the highly invasive and aggressive stage of prostate cancer, including interleukin 6-signal transducer and activator of transcription 3 (gene) (IL-6-STAT3) pathway, seem to be impaired by changes in cholesterol content and/or membrane raft organization.[57] Increases in circulating IL-6[58] and constitutive activation of STAT3[59] in patients suggest that the STAT3 signaling pathway may be one of the factors that promotes the invasiveness of prostate cancer cells. In cell culture experiments, IL-6 has been shown to be an inducer of neuroendocrine properties in prostate cancer cells.[60] Data from Kim *et al.*[57] showed that membrane rafts are involved in STAT3 phosphorylation induced by IL-6, causing its translocation from the cytoplasm to the nucleus, and thus activation of the promoter for a neuroendocrine marker, such as neuron-specific enolase (NSE) and subsequent accumulation of NSE protein. The above-mentioned findings represent another example of membrane raft-dependent cellular signal transduction mechanisms of potential relevance to the progression of human cancers.

In most cases of prostate cancer, metastasis occurs in the bones and lymph nodes. One of the steps that trigger spreading involves chemoattraction of circulating cancer cells toward chemokines released by specific sites.[61] Data show that interaction between chemokine CXCL12 and its receptor CXCR4 can be significant for the metastatic process of prostate cancer cells to bone.[62] Elevated CXCR4 expression became a useful prognostic factor for patients with metastatic prostate cancer undergoing androgen-withdrawal therapy[63] and was found to be associated with membrane rafts in prostate cancer cells.[64] CXCL12 initiates the activation of AKT kinase through membrane raft-associated CXCR4 on the surface of cancer cells. This receptor–ligand interaction activates both the PI3K and MAPK pathways, ultimately leading to the activation of AKT and NF-kB transcription factor, followed by matrix metallopeptidase 9 (*MMP-9*) gene expression and MMP-9 protein release, and resulting in cellular migration and invasion. These findings indicate the potential role of raft domains in the processes of chemoattraction where they give rise to MMP-9-initiated invasion, tumor growth, and bone remodeling in prostate cancer.[64]

Additional studies showed that the CXCL12/CXCR4 interaction transactivates the HER2 receptor in membrane rafts of prostate cancer cells by phosphorylated non-receptor tyrosine kinase Src. Treatment of cells with methyl β-cyclodextrin (MβCD) reduces the level of basal

and CXCL12-mediated phosphorylation of HER2 in membrane rafts. Slightly decreased levels in isolated membrane raft domains, considered to be detergent-resistant membranes, and elevated levels of CXCR4 in the cytosol and membrane fractions were observed upon MβCD treatment of PC-3 prostate cancer cells.[65] These data indicate that intact membrane raft organization is required for CXCL12/CXCR4-triggered transactivation of HER2 and PC-3 cell invasion. Disorganization of membrane raft domains via treatment with destabilizing agents resulted in suppression of basal and CXCL12-mediated chemoinvasion of PC-3 cells, indicating the great importance of membrane raft-dependent signaling in prostate cancer metastasis to the bone tissue.[65] Subsequent studies by Conley-LaComb *et al.*[66] suggested that raft membrane domains are main sites for CXCL12/CXCR4 transactivation of EGFR and HER2 via heterotrimeric G protein subunit Gαi2 and Src kinase in the development of prostate cancer metastasis to bone.

Tumor hypoxia gained significant attention in the context of the potential for tumor metastasis, but the molecular mechanisms involved are not fully resolved. Notch-ligand signaling is responsible for the conversion of the hypoxic stimulus into epithelial–mesenchymal transition, which involves increased cell motility and invasiveness.[67] *In vitro* studies using LNCaP cells showed that hypoxia modifies the levels of cell cholesterol and the membrane raft composition, leading to activation of Notch3. In these conditions, the Notch3 receptor is recruited from the non-raft plasma membrane to the raft domain, where the active complex of γ-secretase is located. In consequence, Notch3 becomes accessible to γ-secretase, which cleaves off the intracellular domain of the receptor (NICD) facilitating its translocation to the nucleus and activation of target genes. These changes correlate with malignancy features appearing *in vitro* and progression of the tumor grade *in vivo* in humans.[68]

Another signaling pathway controlling the invasion and metastasis of most human neoplasms including prostate cancer is the hepatocyte growth factor/c-Met (HGF/c-Met) pathway. Binding of HGF to c-Met stimulates receptor activation by phosphorylation, which recruits anchoring proteins such as GAB1 and subsequently activates the following kinases: MAPK, p38, PI3-K, and JNK. This promotes tumor cell proliferation and changes in morphology and motility associated with metastasis and tumor invasion. Overexpression of both HGF and its receptor c-Met is associated with outcome of prostate cancer and can induce ligand-independent pathways promoting cell division.[69] Treatment of DU-145 prostate cancer cells with cholesterol-lowering agents such as MβCD or simvastatin followed by incubation with HGF confirmed that activation of c-Met and subsequently AKT and ERK kinases is raft dependent.[70] A summary of raft-mediated pathways related to prostate cancer is presented in Figure 1.

Membrane rafts as a target in prostate cancer therapy

Due to their roles in regulating various stages of prostate cancer progression, membrane rafts have attracted attention as interesting targets for cancer treatment and possibly prevention. Plant-derived polyphenols emerged as promising agents against a variety of neoplasms, including roles in prevention and therapy for prostate cancers. For example, tea (-)-epigallocatechin-3-gallate (EGCG) suppresses EGF-, PDGF-, and FGF-derived signal transduction together with downstream kinases such as AKT and ERK, which are activated in cancer cells.[71] Depending on the cell line, the length of treatment, and the administration protocol, EGCG inhibits growth of various prostate cancer cell lines with rather high efficacy: the half maximal inhibitory concentration (IC_{50}) is in the range of 40–80 μM.[72]

Recent data indicate that the anticancer action of green tea catechins (GTCs) is no longer restricted to their direct antioxidant/pro-oxidant properties. The interaction of GTC with cell surface receptors, membrane raft domains, and the ER compartment may affect transcription factors, which leads to a change in the expressions of certain genes or interferes with pro-cancerous mechanisms in the cells.[73]

NMR spectroscopy studies on model membranes indicate direct interaction of EGCG with phospholipids, affecting their dynamics and mobility.[74] Consequently, the EGCG–lipid interaction causes membrane expansion and thinning.[75] EGCG probably alters the organization of membrane rafts by sequestering cholesterol.[70] The aforementioned HGF-stimulated c-Met was found to co-localize with the raft marker protein flotillin in the membrane raft domains. In the DU154 prostate cell line, EGCG at physiologically relevant concentrations inhibits the HGF-controlled c-Met pathway and its downstream targets implicated in invasion and metastasis. At the same time, the decrease in the cholesterol level with MβCD or simvastatin abolished HGF signal transduction in DU145, fibroblast, and lung cancer cells, suggesting that disorganization of membrane raft domains possibly suppresses c-Met signaling and affects cell invasiveness.

Gene therapy using adenovirus vectors provides an interesting opportunity to target castration-resistant prostate cancer. The commonly used approach involves the development of a tissue- or tumor-restricted or specific replicative adenovirus carrying the viral E1a gene under the control of tissue- or tumor-specific promoters. E1a protein plays a key role in regulating the expression of adenoviral genes and viral replication through inactivation of the tumor suppressor pRB and transactivation of the promoters of late genes.[76,77]

Li *et al.* developed an oncolytic prostate-restricted adenovirus, AdE4PSESE1a, for patients with castration-resistant prostate cancer. This approach utilizes two adenoviral genes, such as *EL1a* and *E4*, under the control of a prostate-specific enhancer sequence.[77] In solid tumors, the effectiveness of infection and the distribution of virus in the tissue is limited, so the same group of researchers developed TRAIL-expressing prostate-restricted, replication-competent adenoviral vector (PSRCA).[78] PSRCA through transcription of *E1a*, *E1b*, and *E4* adenoviral genes combined with TRAIL improved the antitumor efficacy of TRAIL against cancer.[78] Furthermore, in androgen-independent CWR22rv tumor xenograft mice, the cholesterol-lowering drug lovastatin improved the

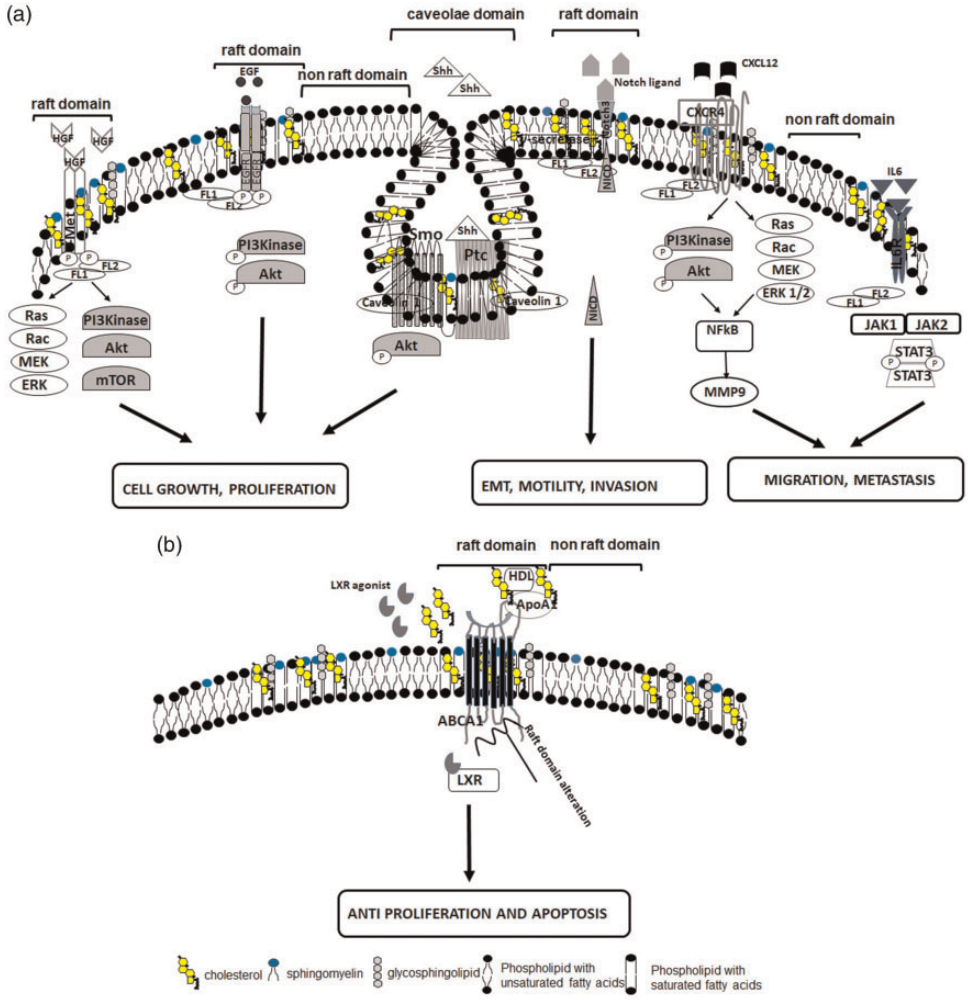

Figure 1. Caveolar and flat membrane raft-mediated pathways in prostate cancer cells. (a) Signaling pathways that promote prostate tumor growth and progression. (b) LXR as a modulator of membrane raft signaling promoting apoptosis in prostate cancer cells. ABCA1: ATP-binding cassette A1 transporter; CXCL12: C-X-C motif chemokine ligand 12; CXCR4: receptor for CXCL12; EGF: epidermal growth factor; EMT: epithelial-mesenchymal transition; ERK 1/2: extracellular signal regulated kinase 1 and 2; FL1 and FL2: flotillins 1 and 2; HDL: high density lipoprotein; HGF: hepatocyte growth factor; JAK1: Janus kinase 1; JAK2: Janus kinase 2; LXR: liver X receptor; MEK: mitogen activated kinase; MMP9: matrix metalloproteinase 9; NFκB: nuclear factor kappa B; Ptc and Smo: patched and smoothened receptor complex; Shh: sonic hedgehog.

antitumor efficacy of PRRA-TRAIL by enhancing tumor growth suppression. Loss of cholesterol in membrane rafts due to lovastatin affects the expression levels of the coxsackie–adenovirus receptor and of integrins, which are all crucial for adenovirus binding and internalization and thus control apoptosis by controlling death receptor expression. These studies showing the dependence of effective adenoviral infection and TRAIL-induced apoptosis on membrane rafts point to these domains as suitable targets for prostate cancer therapy.[77]

Membrane raft research perspective

Although membrane raft research seems to be one of the richest fields in contemporary membrane studies, there is still study required to elucidate the molecular mechanism (s) governing raft organization and regulation. One direction is to search for the proteins involved in raft organization. The answers to this basic question have many further implications for the biological roles of these domains. In neoplastic cell studies, it is critical to understand the quantitative dependence of signal transduction within raft-rich and raft-poor plasma membranes. Proteomic, metabolomics, and interactomic approaches should facilitate great progress in this field.

Conclusions

- Numerous studies have shown that cholesterol accumulation occurs in the cells of solid tumors, including prostate cancer, and this event correlates with the transition to the metastatic state.
- An increase in the cholesterol level in the plasma membrane, whether due to an increase in the bloodstream level or from dysregulated endogenous synthesis, promotes the creation of raft domain precursors and coalescence of raft, which stimulate

signaling pathways involved in prostate cancer growth and progression.

- The results from research utilizing the modification of raft domains to affect the signaling pathways involved in prostate cancer progression and metastasis indicate that membrane rafts domains are a viable target for cancer therapy.
- The green tea polyphenol EGCG, through direct interaction with membrane lipids and deformation of the lipid bilayer, inhibits numerous signaling pathways that contribute to cancer.
- Statins are HMG-CoA reductase inhibitors that are commonly used as a treatment for cardiovascular diseases. They may reduce the risk of several neoplasms, including prostate cancer. Statins have been shown to suppress prostate cancer inflammation, proliferation, migration, and invasion, and to promote apoptosis.
- Further studies on the dependence of prostate cancer development or regression on lateral membrane organization of cancer cells should further our understanding of the role of raft domains in fine-tuning the signaling pathways governing the survival and proliferation of various types of prostate cancer cells.

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