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Alterations in Cellular Cholesterol Content Can Be a Potential Anticancer Strategy

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Abbreviations: PL3K: Phosphatidylinositol 3 Kinase; mTOR: mammalian Target of Rapamycin; SREBP: Sterol Regulatory Element Binding Protein

Introduction

Cholesterol, a unique lipid molecule biosynthesized by all animal cells, is an essential structural constituent in cell membranes to maintain their structural integrity and fluidity. Cholesterol is critical to synthesis of hormones, vitamin D and bile acid, multiple cellular signaling, intracellular transport and a variety of cell functions [1,2]. Cholesterol is necessary to the structure and function of caveolae and clathrin-coated pits, enabling the endocytotic activity [3,4]. In recent decades, increasing lines of evidence show that lipid rafts, which are membrane micro domains assemble glycosphingolipids, protein receptors and kinases, preferentially associate with cholesterol and saturated lipids in driving a wide variety of cellular signaling pathways [5,6]. Not only in normal cellular and physiological functions, intracellular cholesterol homoeostasis once deregulated can be responsible for the development of malignancies through decreasing chemotherapeutic susceptibility and increasing resistance in cancer cells, inhibiting the release of mitochondrial cell death-promoting molecules, activating survival kinases and many other mechanisms [7-9]. Epidemiological studies also have suggested a positive correlation between serum cholesterol levels and cancer risk [9-11]. These studies support the notion that the development of cholesterol-lowering agents can be a potential anticancer strategy.

Deregulation of cellular cholesterol homeostasis by cell survival related kinases

Phosphatidylinositol 3 kinase (PI3K), protein kinase B (Akt) and mammalian target of rapamycin (mTOR) are three serine/threonine-specific protein kinases that coordinately regulate cell cycle, quiescence, transformation, proliferation and survival [12]. Accumulating lines of evidence suggest that cholesterol homeostasis and biosynthesis usually appear to be altered in cancer cells and, once inhibited, the tumor genesis can be blocked indicating that cholesterol content tightly regulates cancer cell fate [13,14]. Recent studies have reported that constitutive activation of PI3K/Akt signaling pathway induces an increase in intracellular cholesterol content in cancer cells through multiple mechanisms, including induction of LDL receptor-related cholesterol import, activation of sterol regulatory element binding protein (SREBP)-dependent cholesterol synthesis and inhibition of ATP-binding cassette transporter ABCA1-regulated mTORC1-dependent cholesterol export [8,15-17]. Further studies reveal that the increase of cholesterol levels is responsible to cancer cell growth, cell survival and cancer aggressiveness and bone metastases [15, 16,18-21]. The mechanism that PI3K/Akt/mTOR pathway regulates intracellular cholesterol levels has been identified, suggesting Niemann-Pick disease type C1 (NPC1) protein serves as a crucial target. NPC1 is a membrane protein which controls intracellular cholesterol trafficking in mammals [22]. Cholesterol binds to NPC1 with hydroxyl group in the binding pocket, leading to the export from the limiting membrane of late endosomes/lysosomes to the endoplasmic reticulum and plasma membrane [23]. Recently, the link between NPC1 degradation and Akt/mTOR pathway has been addressed in several types of cancer [24-26]. It has been demonstrated that inhibition of Akt/mTOR pathway induces a decrease in NPC1 ubiquitination, suggesting a role of Akt/mTOR pathway in NPC1 proteasomal degradation. These studies reveal Akt serving as a key regulator on NPC1 degradation and connect this protein with cancer cell proliferation and migration [24,25]. Moreover, Naren and the colleagues have used U18666A, an inhibitor of NPC1 function, to inhibit cholesterol trafficking to mimic the condition of NPC1 defect in cells, leading to higher NPC1 expression and higher resistance against imatinib mesylate, a chemotherapy medication used to treat chronic myelogenous leukemia [27]. The study suggests that cells with highly expressed NPC1 may have higher resistance to cancer chemotherapeutic agents.

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Major platforms of lipid rafts in organizing multiple cellular survival signals and coupling between membrane microenvironment and drug resistance

Cholesterol also can be an upstream effectors to regulate PI3K/Akt activities. Several studies have reported that the depletion of cholesterol from plasma membranes with beta-cyclodextrins is able to disrupt PI3K/Akt signal transduction [28-30]. The studies also reveal the importance of lipid raft integrity. Lipid rafts are dynamic plasma membrane micro domains which have been implicated in cell survival, proliferation, cell adhesion and invasion and cholesterol metabolism. Lipid rafts can form unique domains with diverse compositions and assist signal transduction through recruiting target proteins in response to intracellular and extracellular stimuli [31-33]. A wide variety of proteins related to cancer development are associated with lipid rafts, including growth factor receptors, serine/threonine protein kinases (PI3K/Akt/mTOR) and integrins [34-36]. Despite lipid rafts are hubs of many critical survival proteins, recent studies have provided evidence suggesting that lipid rafts can also orchestrate death receptor-mediated extrinsic apoptotic signaling [37-39]. The synthetic alkyllysophospholipid edelfosine and derivatives have a high affinity for cholesterol and are trapped in lipid rafts in a number of solid tumors and malignant hematological cells, inducing translocation of death receptors and downstream signaling molecules to these membrane micro domains and eventually leading to apoptosis of cancer cells [39-43]. Edelfosine also can displace PI3K/Akt signal transduction from lipid rafts, inducing PI3K/Akt inhibition. Therefore, lipid rafts can serve as hubs where separation between pro-apoptotic and pro-survival cellular targets can take place [34].

It has been suggested that cancer cells have higher levels of cholesterol-rich lipid rafts compared to those in normal cells. Li and the colleagues have studied and compared the raft levels and effect of methyl-beta cyclodextrin-mediated raft disruption on cell viability of human cancer cell lines versus their normal counterparts. The cholesterol depletion caused apoptosis in human epidermoid carcinoma A431 cells involving decreased raft levels, Akt inactivation, and Bcl-xL down-regulation and caspase-3 activation regardless of epidermal growth factor receptor activation. The Akt activation and cell viability can be rescued by cholesterol replenishment [44]. Notably, they have reported that both breast and prostate cancer cell lines have more lipid rafts which lead to their higher susceptibility to apoptotic stimuli caused by cholesterol depletion [44]. These studies also suggest a potential use of lipid raft-modulating agents in cancer cells those have increased levels of lipid rafts.

Recent studies have addressed the alterations of specific lipid molecules found in cancer cells as well as in tumor microenvironment [45-47]. Moreover, lipid rafts are considered as a center to couple between membrane microenvironment and drug resistance since membrane lipid composition is tightly relevant to the function of ATP-binding cassette transporter P-glycoprotein (Pgp). It has been evident that the Pgp activity is highly sensitive to the presence of cholesterol. However, the membrane fluidity does not solely explain cholesterol-dependent alterations of Pgp-activity. In contrast, accurate lipid raft properties may predominantly be responsible to

the Pgp-transport capacity [48,49]. These studies also support the notion that cholesterol depletion may sensitize chemotherapeutic agents in killing cancer cells through the inhibition of drug resistance. It has been supported by the observations that melittin, a Chinese traditional medicine, sensitizes gemcitabine-induced apoptosis in pancreatic ductal adenocarcinoma cells by down-regulating cholesterol pathway and decreasing drug resistance [50]. Similar study has demonstrated that a ginsenoside derivative, which appears to redistribute lipid rafts and Pgp, results in an accumulation of doxorubicin by decreasing Pgp activity in doxorubicin-resistant cells, leading to chemotherapeutic amplification [51]. These studies suggest that lipid raft-modulating agents may have potential in reducing multidrug resistance activity for chemotherapeutic sensitization.

Anticancer strategies by using cholesterol-depleting or lipid raft-modulating agents

Because of the crucial roles played by cholesterol in cancer development, the interruption of cholesterol supplementation and/or lipid raft integrity can be a potential strategy in the development of cancer chemotherapeutic agents. Statins, well known competitive inhibitors of hydroxymethylglutaryl-CoA reductase enzyme (HMG-CoA reductase), are widely used as cholesterol-lowering agents. In recent decades, much attention has been directed toward the use of statins in oncological therapy. Accumulated cellular and animal studies show an adequate anticancer effect of statins including inhibition of cell proliferation and invasion, and induction of apoptosis and differentiation. Among the statin family, lovastatin, simvastatin, atorvastatin, cerivastatin and fluvastatin have been extensively elucidated and the signaling pathways have been reported regarding the inhibition of PI3K/Akt/mTOR/p70S6K pathway, deregulating cell cycle proteins, blocking MAPK/Erk signaling, activation of JNK pathway, inhibition of RhoA membrane translocation from cytosol, F-actin depolymerization and inhibition of actin stress fiber assembly [52-61]. Statins may also induce a decrease of cholesterol content in lipid raft, suppress caveolin-1 expression in lipid rafts, and induce Fas translocation into lipid rafts, suggesting that statins may trigger apoptotic cell death through the modulation of death receptors in lipid rafts [62]. Furthermore, statins have been studied to inhibit angiogenesis through down-regulation of VEGF, inhibition of endothelial cell proliferation and block of adhesion to extracellular matrix. However, it has been noted that different statin may exert dual and concentration-dependent impact on regulating angiogenic activities of human primary macrovascular endothelial cells [52,63]. Altogether, statins can induce different effects depending on the concentration, duration of exposure of cells to statins, cell lines and the type of statin being used [64].

In cancer patients, the efficacy of statins as chemotherapeutic drugs has been evaluated both in monotherapy and in combinatory therapy with clinical chemotherapeutic drugs [52]. Some clinical studies have demonstrated a positive outcome. Kawata and the colleagues have evaluated the efficacy of pravastatin combined with 5-Fu in patients with unrespectable hepatocellular carcinoma. Results show a significant prolonged survival in statin-treated group [65]. Similar positive effects have been demonstrated in

the report by Graf and the colleagues on the treatment of patients with hepatocellular carcinoma by transarterial chemoembolization combined with pravastatin [66]. Several epidemiologic studies also suggest a positive correlation between increased serum cholesterol content and risk for some cancer types including prostate cancer, melanoma and non-metastatic rectal cancer [15,52,67-69]. On the contrary, some studies show that statins have failed to improve the median survival of patients with certain types of cancer. The meta-analysis of large randomized clinical trials also suggests no association between cholesterol and cancer [15,52,70,71]. Because of the controversy, additional studies are required to connect the mechanism evidence, clinical studies and epidemiological data to solve these problems.

Omega-3 polyunsaturated fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), control some key cellular mechanisms and play a beneficial role in inflammatory diseases. However, the evidence connecting the consumption of omega-3 polyunsaturated fatty acids to a lower cancer risk is insufficient [72] exception possibly of breast cancer [73]. Several studies have reported that EPA and DHA can inhibit cell proliferation and induce apoptosis of MDA-MB-231 human breast cancer cells through the incorporation of these fatty acids into lipid rafts, leading to an activation of p38MAPK and a decrease in EGFR levels in lipid rafts in spite of the accompanied phosphorylation of EGFR [74]. Moreover, both EPA and DHA can reduce surface expression of CXCR4, leading to a decrease of CXCR4-mediated cell migration of MDA-MB-231 cells [75]. These studies have provided evidence that omega-3 polyunsaturated fatty acids can modify lipid raft in both biochemical and biophysical features, decreasing the content of cholesterol and distribution of key proteins [76]. These effects can ultimately induce a decrease of cell proliferation and metastasis, and an increase of apoptosis in breast cancer cells.

Conclusion

From a large body of evidence, lipid raft modifying/cholesterol lowering agents can decrease lipid raft associated pro-survival protein (e.g., growth factor receptors and PI3K, Akt and mTOR kinases) and in induce translocation of death receptors. These impacts can eventually lead to the inhibition of cell proliferation and metastasis, and induction of cell death. However, the solubility, pharmacokinetics and delivery of the high lipophilic agents are key issues to solve. Therefore, several statin-loaded nanoparticles have been developed such as solutol-based lipid nanocapsules and cholic acid core, star-shaped polymer consisting of poly (D,L-lactide-co-glycolide) nanoparticles are able to display good anticancer activities in breast cancer [77,78]. It has been, therefore, suggested that the development of lipid raft modifying/cholesterol lowering agents is a potential anticancer strategy if the solubility and drug delivery can be appropriately solved.

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