

Review Article

Lipid metabolism and carcinogenesis, cancer development

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Abstract: The disorder of lipid metabolism is pathologically linked to hyperlipidemia, lipid storage disease, obesity and other related diseases. Intriguingly, recent studies have revealed that lipid metabolism disorders play an important role in carcinogenesis and development as well, since they cause abnormal expression of various genes, proteins, and dysregulation of cytokines and signaling pathways. More importantly, lipid-lowering drugs and anti-lipid per-oxidation treatment have been showing their advantages in clinic, in comparison with other anti-cancer drugs with high toxicity. Thus, further elucidation of molecular mechanism between lipid metabolism and cancer is essential in developing novel diagnostic biomarkers and therapeutic targets of human cancers.

Keywords: Lipid, lipid metabolism, carcinogenesis, cancer development, cancer treatment

Introduction

Disorder of lipid metabolism is characterized by abnormalities of lipids and lipid metabolites existed predominantly in plasma as well as in other tissues, which is caused by congenital or acquired factors. Classically, lipids are mainly classified into two types: lipid (e.g. phospholipids, glycolipids and sterols, etc.) and fat, such as triglycerides (TG), and sterols also include cholesterol, sex hormones and vitamin D, etc. These lipids are digested, absorbed through small intestine, transformed by liver, stored in adipose tissue, subsequently, served to other tissues when they are in need. TG as important energy storage substance plays a major role in energy supply, thermoregulation, and organism protection combined with skin, bone, muscle and other tissues, as well as assistance in absorption of fat-soluble vitamins and so on. Additionally, phospholipids as the main components of biofilm structures, prevent cell membrane from damage, and promote TG metabolism and degradation of deposited cholesterol. Cholesterol is also the basic component of the cell membrane, which maintains the stability of phospholipids bilayer in cell membrane.

Furthermore, it serves as the precursor of steroid hormones, such as gonadal hormone and adrenal cortex hormones. Therefore, the level of lipids is regulated by various related genes, hormones and enzymes. Abnormalities of related genes, hormones and enzymes lead to lipids metabolism disorders, resulting in cardiovascular disorders (CVD), metabolic diseases and cancers, etc.

In addition to energy supply, lipids also promote cell growth and proliferation. Douglas Hanahan *et al.* proposed that the disorder of energy metabolism might induce malignancies [1]. Recently, the frontier of cancer research has shown that energy metabolism, especially lipid metabolism, is significantly elevated during carcinogenesis. Furthermore, abnormality of lipid metabolism promotes cancer development, invasion and metastasis via multiple signaling pathways which implies that targeting lipid metabolism could be a novel strategy for cancer prevention and treatment.

Lipid metabolism and diseases

It is well known that lipid metabolism is a complex physiological process, involving lipid

Disorder of lipid metabolism and cancer

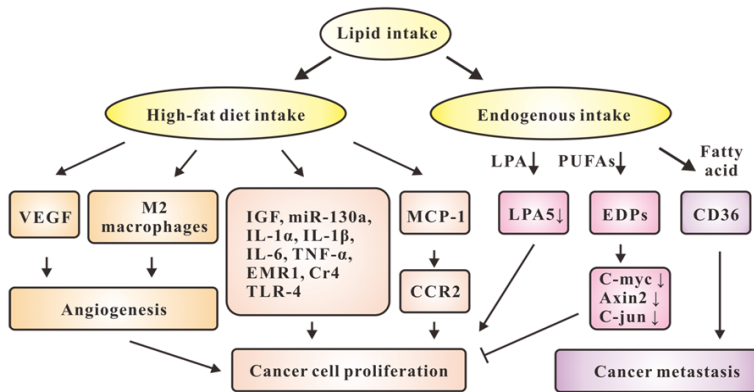


Figure 1. The effects of lipid uptake on cancer cell proliferation and metastasis. Lipid intake includes high-fat diet intake or endogenous intake. Intake of high-fat up-regulates VEGF and promotes the recruitment of M2 macrophages, which promote angiogenesis, thereby accelerate cancer cell proliferation. HFD increases levels of IGF, miR-130a, IL-1 α , IL-1 β , IL-6, TNF- α , EMR1, CR4, and TLR-4, promoting cancer cell proliferation. HFD also accelerates cancer cell proliferation through activation of MCP-1/CCR2 signaling. Endogenous intake includes LPA, PUFAs and fatty acid. Decreased expression of LPA5 accelerates proliferation. PUFAs significantly increase levels of EDPs, which results in reduced expressions of C-myc, Axin2, and C-jun, and inhibition of cancer growth. Intake of fatty acid increases the expression of CD36, which impairs cancer metastasis.

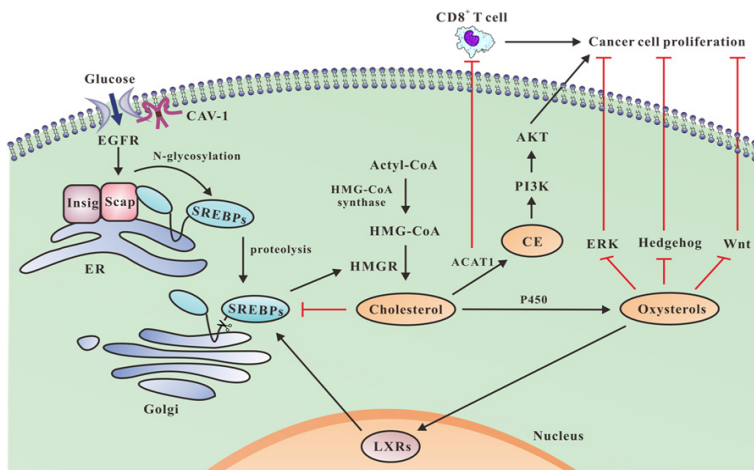


Figure 2. The effects of cholesterol synthesis on cancer cell proliferation. Glucose uptake via CAV-1 promotes EGFR signaling pathway, induces N-glycosylation of SCAP and consequent activation of SREBPs. Upon cholesterol depletion, the nascent SREBPs, embedded in the ER, are transported to the Golgi. SREBPs undergo intramembrane proteolysis under the control of Insig and SCAP to be the hydrolysis products of SREBPs, which up-regulate HMGR to promote cholesterol synthesis. Oxysterols produced by cytochrome P450 enzyme-mediated cholesterol oxidation reaction, lead to up-regulation of SREBPs since they up-regulate LXRs, and thereby stimulate HMGR. Oxysterols slow down proliferation by interfering with ERK, Hedgehog and Wnt pathways. ACAT1 catalyzes cholesterol esterification leads to activation of PI3K/AKT pathway, thus, significantly promotes cancer proliferation. Moreover, ACAT1 inhibits proliferation of CD8⁺ T cells, promoting cancer growth.

and *de novo* synthesis of acetyl coenzyme A *in vivo*. Consistently, high expression of fatty acid synthase (FASN) has been observed in cancer cells [2, 3]. In mammals, FASN is an important enzyme with six catalytic domains, which catalyzes the synthesis of endogenous long chain fatty acid. FASN converts dietary carbohydrates to long chain saturated fatty acids through acetyl-CoA, malonyl-CoA and nicotinamide adenine dinucleotide phosphate (NADPH) [4]. Abnormally elevated cholesterol levels may be attributed to sterol-regulatory element binding proteins (SREBPs) mediated by 3-hydroxy-3-methyl glutaryl coenzyme A reductase (HMGR) in cancer cells. Upon cholesterol depletion, nascent SREBPs embedded in the endoplasmic reticulum (ER), are transported to the Golgi apparatus, where nascent SREBPs undergo intramembrane proteolysis under the control of Insulin-induced gene (Insig) and SREBP cleavage-activating protein (SCAP). Then up-regulated HMGR regulates cholesterol synthesis [5] (**Figure 2**). The mevalonate pathway catalyzed by HMGR is one of the main pathways to produce sterols as well [6]. Conversely, excessive accumulation of intracellular oxysterols results in up-regulation of liver X receptors (LXRs), and thus stimulates SREBPs (**Figure 2**). LXRs belong to nuclear receptor subfamily of ligand-activated transcription factors, including LXR α and LXR β . The activation of LXR α and LXR β up-regulates the expression of the related proteins, such as SREBP-1C (a subtype of SREBP) and ATP-binding cassette transporter A1 (ABCA1), thereby regulating lipid synthesis, transportation

intake, synthesis and transportation, and so on. Lipids are mainly derived from food intake

and thus stimulating cancer cell proliferation.

and so on. LXRs belong to nuclear receptor sub-family of ligand-activated transcription factors, including LXR α and LXR β . The activation of LXR α and LXR β up-regulates the expression of the related proteins, such as SREBP-1C (a sub-type of SREBP) and ABCA1, thereby regulating lipid synthesis, transportation and so on. LXRs are also the regulatory hub of multiple metabolic pathways, including fatty acid, cholesterol and energy metabolism [7, 8]. For example, up-regulated expression of SREBPs promotes lipid synthesis, while as, up-regulated expression of ABCA1 accelerates intracellular cholesterol efflux.

The key to maintain lipid homeostasis is whether excessive intracellular uptake or synthesis of lipids can be metabolized or transported to be outside of the cell membrane. Similarly, lipid efflux also involves multiple proteins, including ABCA1, Apolipoprotein (Apo) A-1, ApoE, peroxisome proliferators-activated receptors (PPARs), Scavenger receptor class B type 1 (SR-B1) and Caveolin-1 (Cav-1), etc. ABCA1 is mainly involved in the regulation of reverse cholesterol transport and prevention of type II diabetes mellitus (T2DM) and atherosclerosis (AS) [9]. Binding of ApoA-1 to ABCA1 may also enhance the activity of lipid-transport pathway. In addition to the known role of ApoA-1 as the key carrier of high density lipoprotein (HDL) and cholesterol receptor, it also enhances HDL influx and cholesterol efflux. Furthermore, it promotes excessive cholesterol excretion from peripheral liver tissue. It is reported that higher levels of plasma cholesterol are associated with lower risk of Parkinson's disease, indicating that abnormal lipid metabolism may be closely correlated with neurodegenerative diseases [10]. Moreover, ApoA-1 up-regulation can promote glioblastoma cell apoptosis and necrosis [11]. Furthermore, PPARs induce over-expression of HDL receptors, such as SR-B1 and ABCA1 which accelerate cellular cholesterol efflux. The nuclear receptors PPARs include three isotopes, α , β/δ and γ , which orchestrate lipid synthesis and cholesterol metabolism, reducing the incidence of nonalcoholic fatty liver disease and liver cancer [12].

Dyslipidemia, in particular, elevated levels of serum lipid and up-regulation of lipoproteins, have been considered to be the common pathology of various diseases, such as obesity, T2DM and hepatitis [13]. Increased levels of

low density lipoprotein (LDL) and serum total cholesterol (TC) and decreased level of HDL not only result in AS, but also lead to coronary heart diseases and brain infarction [14]. Taken together, lipid metabolic disorders are involved in pathologies of various diseases directly or indirectly.

Abnormal levels of lipid and carcinogenesis, cancer development

Numerous of studies have demonstrated that abnormal levels of lipids are intimately related to carcinogenesis and cancer metastasis. Malignant transformation and accelerated of cancer cell proliferation is in high demand of energy, which induces alterations in lipid metabolism to allow the survival of cancer cells [15]. Based on clinic pathological study of breast cancer, researchers have found that plasma levels of TC, TG, HDL and LDL of breast cancer patients were significantly higher than that of control group. In addition, TC and TG levels of patients with metastasis were significantly higher than that of patients without lymphatic metastasis [16]. Further study has showed that cholesterol ester (CE) accumulation promotes breast cancer cell proliferation. These results highlight intratumoral CE accumulation as a potential indicator in diagnosis of human breast cancer [17]. Moreover, increased free fatty acids (FFAs) not only induce the expression of plasminogen activator inhibitor-1 (PAI-1) in breast cancer cells, but also inhibit the degradation of fibrin, facilitating breast cancer invasion and metastasis [18]. Meanwhile, LDL and very low-density lipoprotein (VLDL) is in favor of breast cancer progression and metastasis through protein kinase B (AKT)-induced epithelial-mesenchymal transition (EMT) and cancer angiogenesis [19]. Experiments *in vivo* confirmed the link between cholesterol, androgen levels and prostate cancer [20]. In addition to being a necessary precursor of androgen, cholesterol activates signaling pathways of cancer proliferation, promoting prostate cancer progression. Biochemical study showed that CE accumulation was a consequence of phosphoinositide-3-kinase (PI3K)/AKT pathway activation in cancer cells, thus, promoting prostate cancer progression (**Figure 2**). Metastasis to the bone is one of important features of prostate cancer with poor prognosis [21]. Elin Thysell *et al.* pointed out that the mean levels of cholesterol of prostate cancer

Disorder of lipid metabolism and cancer

Table 1. Abnormal lipids levels and carcinogenesis, cancer development

Lipid/Lipoprotein	Level	The types of cancers	Effect	References
TC	↑	Prostate cancer, colorectal cancer, breast cancer	Carcinogenesis risk↑	[16, 24]
		Gastric cancer, liver cancer, lung cancer	Prognosis risk↓	[25]
TG	↑	Small cell lung cancer, pancreatic cancer, ovarian cancer, breast cancer, gastric cancer	Carcinogenesis risk↑	[16, 29]
CE	↑	Breast cancer, prostate cancer	Cell Proliferation↑	[17, 21]
LDL	↑	Non-small cell lung cancer, breast cancer, colorectal cancer	Prognosis risk↑	[28, 29]
VLDL	↑	Breast cancer	Angiogenesis↑	[19]
HDL	↑	Colorectal cancer	Carcinogenesis risk↑	[16]
FFAs	↑	Breast cancer	Metastasis↑	[18]
ApoE	↑	Lung adenocarcinoma, stomach cancer	Metastasis↑	[28-30]
ApoA-1	↑	Glioblastoma, leukemia	Carcinogenesis risk↓	[11, 29]

↑-up-regulation, ↓-down-regulation.

patients with bone metastases was 127.30 mg/g as compared to 81.06 in that of patients with bone metastases from different origin and 35.85 mg/g in that of normal bone [22]. These data suggested that high levels of cholesterol might contribute to the metastases of prostate cancer into bone.

Previous studies have reported that higher levels of TC are associated with higher prevalence of colorectal cancer [23]. Consistently, the level of TC decreased by absorbance of polyunsaturated fatty acids from dietary led to lower risk of colorectal cancer [24]. In some prospective studies, TC level was positively associated with breast, prostate and colon cancers. On the other hand, TC levels were negatively associated with liver, stomach and lung cancer [25]. Studies reported that nearly two-fifths of the patients (41.3%) of colorectal cancer exhibited elevated LDL level while most patients (88.3%) showed normal HDL levels [26, 27]. In addition, declined HDL and elevated LDL were associated with poor prognostic outcomes in metastatic colorectal cancer patient. In consistent, HDL prevented the development of metastatic colorectal cancer while LDL promoted its development. Ting *et al.* demonstrated that reduced levels of LDL and LDL receptor (LDLR) prevented malignant development of small-cell lung cancer [28]. Both LDL and LDLR are favorable prognostic factors for the survival of patients with small-cell lung cancer. 50% of the children who had acute lymphoblastic leukemia displayed dyslipidemia, were the characteristic with raised serum TG and LDL, as well as decreased HDL and TC [29]. Moreover, ApoE has been shown to be associated with development and metastasis of lung

adenocarcinoma and gastric cancer [30, 31]. A recent study showed that ApoE levels were three times higher in cells with lymph node metastases (LNM) than that of cells without LNM, which indicated that ApoE was a candidate biomarker for lung adenocarcinoma metastasis [30]. Additionally, ApoE is also predominantly expressed in gastric cancer. Cancers with high ApoE expression are able to invade deeply into the muscle layer, the serosal layer, or show more positive lymph node metastasis [31]. Therefore, abnormal lipid levels are intimately associated with the occurrence, development and metastasis of many types of cancers. The quantities of lipids and lipoprotein are associated with the risk or prognosis of cancer (Table 1).

Lipids metabolism and carcinogenesis, cancer development

Lipid intake and carcinogenesis, cancer development

Generally, human cells intake fatty acids from two sources: diet intake or endogenous intake. Based on previous studies, excessive fatty acids intake from diet was considered to be the main factor causing carcinogenesis and cancer development. Han *et al.* found that high-fat diet (HFD) increased the incidence of poorly differentiated carcinoma in transgenic adenocarcinoma mouse prostate model, which was accompanied by up-regulation of proteins associated with cell proliferation and angiogenesis, such as vascular endothelial growth factor (VEGF), thereby reducing the survival rate of the mice [32]. Recent reports showed that HFD accelerated growth and proliferation of pros-

tate cancer cells through activation of monocyte chemoattractant protein (MCP)-1/CC chemokine receptor 2 (CCR2) signaling [33]. HFD increased the level of insulin-like growth factors (IGF), inducing prostate cancer [34]. Nevertheless, microRNA (miR)-130a was attenuated in HFD-induced prostate cancer proliferation [35].

Moreover, excessive intake of lipids promotes cancer development by inducing inflammatory response. HFD promotes progression of prostate cancer attributing to increased levels of pro-inflammatory cytokines, such as interleukin (IL)-1 α , IL-1 β , IL-6, and tumor necrosis factor (TNF)- α [36]. In addition, increased macrophage markers were observed during consumption of HFD, such as EGF-like module-containing mucin-like hormone receptor-like 1 (EMR1), complement receptor 4 (CR4) and toll-like receptor (TLR)-4, and inflammatory cytokines in the adipose tissue, which provided evidence for the link between HFD consumption and increased risk of colon cancer [37]. M2 macrophages are used for various forms of alternatively activated macrophages resulting from monocyte exposure to IL-4 or IL-13, immune complexes/TLR ligands, IL-10 or glucocorticoids [38]. HFD reduced cancer cell apoptosis and increased recruitment of total and M2 macrophages into epithelial tumors, which promoted cell proliferation, angiogenesis, thereby leading to increased incidence of breast cancer [15].

Consistently, a study published in *Nature* reported that excessive lipid intake increased the expression of B-scavenger receptor (CD36), a member of cell surface fatty acid receptors. Clinically, inhibition of CD36 reduces the metastasis of human melanoma and breast cancer [39] (**Figure 1**). Recently, lysophosphatidic acid (LPA) has attracted attention as a key regulator of colorectal cancer, which has diverse pathophysiological functions such as proliferation and infiltration of mammalian cancerous cells mechanically due to the decreased expression of mRNA encoding LPA5, one of G protein-coupled receptors [40]. Dietary feeding of ω -3 polyunsaturated fatty acids (PUFAs) significantly increases levels of epoxydocosapentaenoic acids (EDPs), metabolites of ω -3PUFA produced by cytochrome P450 enzymes in plasma and tumor tissue, with reduced expressions of pro-

oncogenic genes such as C-myc, Axin2, and C-jun in cancer tissues, inhibiting colorectal cancer growth [41]. Taken together, lipid intake has significant effects on cancer cell proliferation (**Figure 1**). However, the underlying mechanisms need to be further elucidated.

Lipids synthesis and carcinogenesis, cancer development

In healthy adults, most types of tissues take advantages of dietary fatty acids to function properly, except liver cells and adipose tissue as well as specific physiologic processes, such as endometrial cell proliferation, which use *de novo* synthesis to generate fatty acids [42]. *De novo* lipids synthesis provides a constant energy supply, which is essential for cancer cell growth and proliferation [43]. Cholesterol synthesis starts with acetyl-CoA, which takes two steps to convert to 3-hydroxy-3 methyl glutaryl CoA (HMG-CoA) via HMG-CoA synthase, and then transformed into mevalonate via rate-limiting enzyme HMGR. Cholesterol is easily oxidized when it is exposed to the air. However, whether auto-oxidation of cholesterol exists *in vivo* is controversial. Oxysterols are thought to be generated in the rate in proportion to that of cholesterol synthesis. Oxysterols is the oxidized products of the oxidation reaction mediated by enzyme cytochrome P450. Oxysterols interfere with the process of cell proliferation, resulting in cell death of various cancers, such as leukemia, glioblastoma, colon, breast and prostate cancer, while they have little or no effect on senescent cells. Oxysterols regulate the transcription of the key enzyme HMGR in cholesterol synthesis by binding to Insig-1, Insig-2 and LXRs. Oxysterols slow down cell proliferation as well as stimulate cell death by interfering with ERK, Hedgehog and Wnt pathways [44]. Glucose metabolites, which are normally used for ATP production, are redirected to be used in lipid synthesis via the pentose pathways. Both the metabolic rate and glucose uptake are increased to maintain the faster proliferation of cancer cells. This atypical metabolic process is known as the Warburg effect [45]. Cheng *et al.* documented that glucose uptake via CAV-1 enhanced epidermal growth factor receptor (EGFR) signaling pathway, which induced N-glycosylation of SCAP and consequent activation of SREBPs. SCAP is the key glucose-responsive protein serving as the oncogenic

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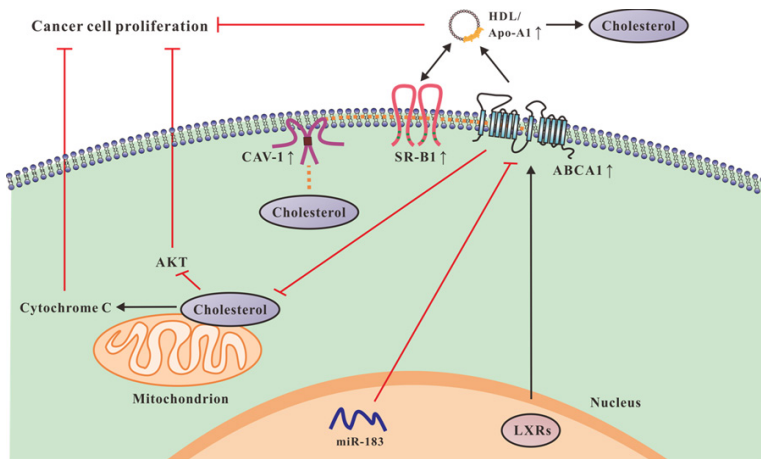


Figure 3. The effects of cholesterol transportation on cancer cell proliferation. ABCA1 inhibits accumulation of mitochondrial cholesterol, which leads to increased release of cytochrome C and inhibition of AKT signaling, impairing cancer cell proliferation. MiR-183 promotes proliferation by degrading ABCA1 in cancer cells. LXRs increase ABCA1-mediated cholesterol efflux, resulting in cancer regression. In addition, CAV-1 complex subsystem transports cholesterol from intracellular compartments to caveolae, both subsystems of SR-B1 and ABCA1 transfer cholesterol from CAV-1 to extracellular HDL/ApoA-1. A network regulates the four systems and the entire transportation process. The elevated expressions of CAV-1, SR-B1, ABCA1 and HDL/ApoA-1 accelerate cholesterol efflux, which lead to inhibition of cancer cell proliferation.

signaling hub and fueling for SREBP-dependent lipogenesis. Blockade of SCAP N-glycosylation ameliorates EGFR-driven glioblastoma growth [46] (Figure 2). The available evidences suggested that SREBP-1 not only enhanced cholesterol biosynthesis, but also promoted invasion and metastasis of breast cancer [47] and glioblastoma [48]. Previous study by Pizer *et al.* showed that fatty acid synthesis was heavily inhibited in human acute promyelocytic leukemia HL60 cells upon culture condition of serum-free and fatty acid-free medium [49]. However, compared with normal cells, the expression of FASN is higher in breast cancer, colon cancer, prostate cancer, melanoma, lung cancer, bladder cancer, ovarian cancer, gastric cancer, endometrial cancer, kidney cancer, skin cancer, pancreatic cancer, head and neck cancer and tongue cancer [50-52]. FASN plays a crucial role in EMT, a process that the epithelial cells transited to mesenchymal cell type. The close relationship between EMT and cancer development and metastasis has been well documented. It was corroborated by study that the expression of FASN during EMT, while silence of FASN might reverse EMT [50]. In addition, Acetyl CoA carboxylase (ACC) is the rate-limiting enzyme in fatty acid synthesis,

which also plays a pivotal role in carcinogenesis and development. In preclinical models, ACC is required for the *de novo* fatty acid synthesis for the growth and viability of non-small-cell lung cancer cells [53]. Down-regulation of CE in T cells by genetic ablation or pharmacological inhibition of Acetyl-Coenzyme A acetyl transferase 1 (ACAT1), a key cholesterol esterification enzyme, led to potentiated effector function and enhanced proliferation of CD8+T cells and increased cholesterol level, resulting in the inhibition of the growth and metastasis of melanoma [54] (Figure 2).

Lipid transport and carcinogenesis, cancer development

Our group proposed a novel model of cholesterol efflux from lipid-loaded cells including

four subsystems and one center coupled to each other [55]. The novel model consists of intracellular trafficking subsystem of CAV-1 complex, transmembrane transporting subsystem of ABCA1 complex, transmembrane transporting subsystem of SR-B1 complex, extracellular trafficking subsystem of HDL/Apo-A1 and CAV transporting center. In brief, the CAV-1 system transports cholesterol from intracellular compartments to caveolae. Subsequently, both ABCA1 and SR-B1 complex systems transfer cholesterol from caveolae to extracellular HDL/Apo-A1. These four subsystems are orchestra together as a functional overall system of cholesterol efflux (Figure 3). Our group for the first time puzzled together the network of various key proteins responsible for cholesterol transportation. The transmembrane subtransport system with ABCA1 is the core of overall lipid transportation. The deficiency of ABCA1 allows for accumulation of mitochondrial cholesterol, inhibiting the release of mitochondrial cell death-promoting molecules, such as cytochrome C, and thus facilitating cancer cell survival [56]. MiR-183, targeting the 3'UTR of ABCA1 mRNA, increases intracellular cholesterol. MiR-183 both promotes the proliferation and inhibits the apoptosis of colon cancer cells

Disorder of lipid metabolism and cancer

Table 2. The relationships between lipid metabolism and carcinogenesis, cancer development

Lipid metabolism process	Factors	Effect	References
Lipid intake	CD36↓	(-) Melanoma and breast cancer growth and metastasis	[39]
	LPA↑	(-) Colorectal cancer proliferation	[40]
	C-myc↓Axin2↓C-jun↓	(-) Colorectal cancer growth	[41]
Lipid synthesis	SREBP↓	(-) Breast cancer and glioblastoma metastasis	[45-47]
	ACAT1↑	(-) Melanoma growth	[53]
	ACC↑	(-) Non-small cell lung cancer growth	[50]
	FASN↓	(-) Colon, prostate, breast, lung, kidney, ovary, bladder, endometrium, skin, pancreas, tongue, head and neck cancer invasion and metastasis	[48-51]
Lipid transportation	ABCA1↑	(-) Colon, ovary, prostate, oral cancer growth	[8, 55-57, 59]
	CAV-1↑	(-) Colon cancer growth	[65]
	SR-B1↑	(-) Prostate, ovarian cancer growth and metastasis	[63]
	PPAR↑	(-) Liver cancer growth	[62]
	LXRs↑	(-) Oral cancer, hepatocellular carcinoma and glioblastoma growth	[8, 60, 61]

↑-up-regulation, ↓-down-regulation, (-) -inhibition.

by degrading ABCA1 [57]. Likewise, the reduced expression of ABCA1 due to promoter hypermethylation increases cholesterol levels, promoting cell growth of ovarian cancer cell lines A2780 and CP70 [58]. ABC transporters are widely expressed in epithelial cells of normal mammary gland, but ABCA1 is hardly expressed in breast cancer cells [59]. Meanwhile, several studies have described a closely link between ABCA1 and prostate cancer. Intracellular cholesterol is a substrate for *de novo* androgen synthesis under regulation of AKT signaling, promoting prostate cancer progression. Silence of ABCA1 due to hypermethylation directly leads to high intracellular cholesterol levels, contributing to prostate cancer progression [60]. Remarkable, previous study highlighted that the ABCA1-accelerated cholesterol efflux was critical for LXRs inhibition in human oral squamous cell carcinoma cells [8]. In particular, glioblastoma, a type of highly lethal brain cancer, requires cholesterol for its survival. However, LXR-623, a LXR α -partial/LXR β -full agonist with brain-penetration, selectively kills glioblastoma cells in an LXR β and cholesterol-dependent manner, resulting in tumor regression and prolonged patient survival [61]. Meanwhile, previous study has identified that the synthetic LXR agonist GW3965 potently suppresses glioblastoma growth in glioblastoma xenograft model *in vivo*. Targeting LDLR by using the LXR agonist GW3965 causes inducible degradation of LDLR and increases ABCA1-mediated cholesterol efflux, potently promoting cancer cell death [62]. Moreover, down-regulation of PPAR γ resulted in an obvious decrease in lipid accumulation, thereby inhibiting the

growth of hepatocellular carcinoma in xenograft model in nude mice [63]. Interestingly, SR-B1 is observed to bind to HDL with high affinity to mediate selective cellular uptake and efflux of CE from the lipoprotein core. SR-B1 is also implicated in cholesterol metabolism of cancer cells, whereby over-expression of SR-B1 has been observed in a number of cancer cell lines, including breast and prostate cancers [64]. Cell endocytosis of CAV-1 has been thought to be associated with membrane proteins, extracellular matrix tissue, cholesterol distribution and cell signaling. CAV-1 regulates cell metabolism mainly targeting glycolysis, mitochondrial bioenergetics, glutaminolysis, fatty acid metabolism, and autophagy, which is tightly linked to carcinogenesis and development [65]. Epigenetic profile analysis showed that promoter methylation of CAV-1 gene led to CAV-1 silence, thereby promoting colon cancer cells growth (Figure 3) [66]. How the involved proteins, enzymes or genes during the process of lipid metabolism coordinate together to contribute to carcinogenesis, and cancer development are summarized in Table 2.

The application of drugs targeting lipid metabolism in cancers

Lipid-lowering drugs in the treatment of the cancers

Recently, Lipid-lowering drugs such as statins used alone or in combination with therapeutic agents have been being studied more.

Statins are HMGR inhibitors that inhibit mevalonate in cells through competitive inhibition of

endogenous cholesterol synthesis rate-limiting enzyme, thereby resulting in reduction of intracellular cholesterol synthesis. Then, the feedback from cholesterol improves the number and activity of LDLR, predominantly in liver cells [67]. The application of the synthetic statins in the treatment of various human malignancies has shown promising outcome based on numerous *in vitro* and *in vivo* studies. Statins disturb lipid metabolism and subsequently interfere with signaling pathways of cell proliferation and cell survival, leading to cell apoptosis [68]. Statins reduce serum TC levels and activate liver tissue LDLR by interfering with intracellular lipid oxidative stress, effectively inhibiting cell proliferation of breast cancer [69]. A previous study found that statins induced accumulation of cytosolic lipid droplets as well as up-regulation of ABCA7 and triacylglycerol and phospholipids synthesis (such as 1-acylglycerol-3-phosphate O-acyltransferase 2) during the apoptotic process of pancreatic cancer cells *in vitro* [70]. Furthermore, statins decrease cancer cell proliferation by inhibiting the synthesis of cholesterol, which is essential for new membrane formation in rapidly proliferating cells [71].

Most strikingly, statins in combination with other agents has been clinically applied. For instance, the combination of prostate-restricted replication competent adenovirus-mediated TRAIL with lovastatin, as a potential treatment for advanced prostate cancer, enhances TRAIL-induced apoptosis by depleting cholesterol of lipid rafts and influencing the expression of death receptor, coxsackievirus receptor and adenovirus receptor in prostate cancer cells [72]. Additionally, the combined treatment of eicosapentaenoic acid and lovastatin enhances the regulatory effect on gene expression of HMGCR and LDLR, thereby inhibits hepatocarcinoma cell proliferation [73]. The combination of tamoxifen and lovastatin results in a synergistic stimulation of the LDL receptor activity, which probably blocks sterol synthesis. Based on these results, the simultaneous inhibition of sterol biosynthesis and intracellular cholesterol transportation appears to be an efficient way to treat breast cancer [74]. In addition, a preclinical study demonstrates that the cholesterol-uptake inhibitor ezetimibe reduces serum cholesterol levels, which may prevent prostate cancer growth by inhibiting tumor angiogenesis [75].

Anti-lipid per-oxidation drugs in the application of the cancers

Lipid per-oxidation is a free radical chain reaction process of the oxidative degradation of unsaturated fatty acids. The reaction consists of three major steps: initiation, propagation and termination. And in the initiative step, a fatty acid radical is produced. In the step of propagation numerous free radicals are produced, such as lipid peroxy radicals, lipid oxygen free radicals and lipid free radicals, etc. More importantly, during the termination step various small molecules are produced, which induce oncogenic mutations and activate oncogenic pathways, promoting carcinogenesis [76]. Therefore, agents with antioxidant activity are considered as an important strategy for cancer prevention and treatment [77]. Probuco, as an antioxidant has long been used for the treatment of hypercholesterolemia and anti-lipid per-oxidation in clinic. Probuco inhibits cholesterol efflux from normal human skin fibroblasts without interference with SR-B1-mediated efflux, as well as inhibits ABCA1 translocation to the plasma membrane [78]. Further, probuco is considered to protect lipids and LDL from oxidation, which potentially inhibits angiogenesis, which has an anti-carcinogenic effect on human head and neck squamous carcinoma cells [79]. Probuco not only decreases plasma levels of LDL and HDL, but also increases selective uptake of CE, thereby inhibiting hepatoma cells growth [80]. In particularly, high concentration of probuco significantly inhibits the metastasis of breast cancer into lung [81].

Nowadays, various active substances from traditional Chinese medicine have showed excellence antioxidant effects, such as celastrol, curcumin, quercetin, berberine, etc. They all have effect on inhibition of carcinogenesis and development through anti-lipid per-oxidation activities. Celastrol isolated from the traditional Chinese medicinal herb *Tripterygium wilfordii* Hook.f (Thunder God's Vine), has shown its anti-invasive and anti-metastatic activities in preclinical models of prostate cancer, breast cancer, colon cancer and pancreatic cancer [82]. Celastrol as a very potent inhibitor of lipid per-oxidation effectively reduces lipid accumulation and serum LDL levels [83]. Moreover, celastrol is able to effectively cause weight loss and attenuate high fat mediated oxidative

injury by up-regulating ABCA1 expression, reducing the levels of TC, TG, LDL and ApoB in plasma, increasing antioxidant enzymes activities and inhibiting NADPH oxidase activity, furthermore, decreasing the serum levels of malondialdehyde (MDA) and reactive oxygen species (ROS) in dose-dependent way [84].

Besides, curcumin is a diketone active ingredient isolated from turmeric in Chinese medicine. Because of its excellent anti-proliferative and anti-lipid per-oxidation activity, it has been widely used in the treatment of cancer and related disease caused by the damage of ROS and reactive nitrogen species (RNS). Curcumin has been studied in numerous cancers, including colorectal, cervical, uterus, ovary, prostate, breast, lung, stomach, pancreas, bladder, oral, esophagus cancer and osteocarcinoma [85]. Curcumin enhances the effects of chemotherapeutic agents against glioblastoma multiforme through its inhibition of lipid droplet accumulation [86]. Curcumin also inhibits occurrence and development of multiple cancers by provoking the PPAR γ -LXR-ABCA1 pathway-mediated cholesterol efflux from adipocytes [87].

Quercetin is a polyphenolic flavonoid compound, whose anti-lipid oxidative activity has been taken advantage in cancer treatment. Quercetin effectively decreases the expression of FASN, inhibiting proliferation of nasopharyngeal carcinoma cells, of human gastric cancer cells and of human leukemia T-cells [88]. In addition, quercetin significantly improves the plasma nonenzymatic antioxidant capacity and reduces lipid peroxidation, protecting from oxidative damage evoked by doxorubicin and docetaxel during the treatment of breast cancer [89]. Quercetin also elevates lipid peroxides and thus reduces the tumor size and the cumulative number of papillomas [90]. The study from Sharmila specifically indicated that quercetin treatment prevented the lipid peroxidation and maintains H₂O₂ level, thereby inhibiting the development of prostate cancer [91].

Berberine, alkaloid extracted from berberine, cork and three needles, has been used for cancer treatment. Berberine inhibits lipid accumulation by up-regulating LDLR, resulting in inhibition of human hepatoma cells growth [92]. Berberine regulates lipid metabolism through the inhibition of AMP activated protein kinase (AMPK), FASN, and 5-tetradecyloxy-2-furoic

acid (TOFA), inducing breast cancer cells apoptosis [93]. Berberine significantly attenuates lipid per-oxidation and enhances the anti-oxidative capabilities. Thus, berberine inhibits neoplastic transformation by the induction of antioxidant defense system and then induces apoptosis [94].

Conclusion and prospect

Preclinical cancer studies and clinical trials have revealed the crucial role of lipid metabolism in tumor growth and metastasis. Lipid metabolism and cell survival or proliferation of cancers shares certain common pathways involving numerous proteins as well as various cells, tissues and organelles. Abnormalities in these pathways lead to tumor growth. Based on these findings, many drugs targeting lipid metabolism have been developed for cancer treatment. However, some inhibitors are able to inhibit cancer cell proliferation and tumor growth but they induce cytotoxicity of normal cells as well. Thus, it is particularly important to develop a number of drugs with high specificities, thus decreasing toxicities. However, there are existing challenges: 1) Specific rodent cancer models with hyperlipidemia need to be further established; 2) The molecular mechanism of lipids and lipid oxidation underlying tumor development has not been fully understood; 3) The clinical studies of lipid metabolism and carcinogenesis need further epidemiological analysis. More and more novel molecular targets of lipid metabolism would be identified upon further effort, improving the efficacy on cancer prevention and treatment. In conclusion, further studies are required to understand lipid metabolism of cancer cells both big picture and detail oriented, which will provide effective clinical therapeutic strategies targeting against cancers, the top human health threat.

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Disclosure of conflict of interest

None.

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