Linking Lipid Metabolism with Cell Transformation and Tumor Progression

Meng Si Zuo, Jia Yu Yang, Pei Yun Wang, Hai Ou Yang, Yi Ba

Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin’s Clinical Research Center for Cancer, Tianjin 300060, China

Abstract: Carbohydrates, lipids, and proteins are the three major nutrients required by the human body. The lipids, comprising triglycerides, phospholipids, and sterols, provide energy and essential fatty acids for the body, and are required for the growth and maintenance of human cells and tissues. A variety of lipid molecules and their intermediates are involved in cell signaling and inflammation, and have been reported to promote tumor transformation and progression. Fatty acid biosynthetic enzymes are also involved in the lipid metabolism of tumors. Dyslipidemia is closely related to many solid tumors, and may both play a role in both tumorigenesis and be a consequence of tumor development. Therefore, abnormal lipid metabolism is strongly associated with tumor transformation and progression. This review discusses the signaling pathways, related genes, enzymes, and inflammatory cell factors involved in tumor lipid metabolism, as well as the roles of dyslipidemia in tumor transformation and progression. We believe the information provided will serve as valuable reference highlighting molecules that can be targeted to improve the treatment of tumors.

Key words: Tumor; Lipid metabolism; Lipid raft; Tumor microenvironment

Introduction

The metabolic activity of malignant cells is different from that of non-transformed cells, so metabolic reprogramming represents an important sign of malignancy. Tumor growth may alter glucose, glutamine and lipid metabolism to meet the biosynthetic and energy requirements of tumor cell proliferation. In addition to the Warburg effect, abnormal lipid metabolism is observed in many tumor cells. Lipids provide a great deal of energy for tumor cell proliferation, and are essential to maintain the membrane synthesis and other related functions during cancer cell growth. In this paper, we outline the signaling pathways, related genes, enzymes, and inflammatory factors involved in tumor lipid metabolism. We also describe several solid tumors closely related to dyslipidemia, and describe its relations to tumor transformation and progression (Figure 1).

Cell signaling and gene expression related to tumor lipid metabolism

The functions of lipid rafts and raft-associated proteins

Lipid rafts are microdomains established through specialized membrane patches in the plasma membrane. They are enriched in cholesterol and sphingolipids, and have been demonstrated to participate in signal transduction and protein sorting [1]. Flotillins are highly conserved proteins that can serve as biomarkers of lipid rafts. Flotillin-1 and flotillin-2 form microdomains with specific cholesterol enrichment in the cell membrane. They are related to various signal transduction pathways, cell attachment and membrane transport, and participate in tumor progression and metastasis [2]. Flotillins are associated with a variety of signal transduction pathways, including epidermal growth factor receptor (EGFR), fibroblast growth factor receptor (FGFR), neurotrophin, and insulin signaling [3]. Previous studies have shown that flotillins are involved in multiple cancers. For example, Berger T et al. used flotillin-2 knockout mice to confirm that a lack of flotillin-2 can lead to a decrease in the flotillin-1 protein level and the complete loss of specific membrane microdomains of flotillins [4]. In breast cancer, flotillin-2 knockdown significantly reduced lung metastasis formation, but had no effect on the primary tumor, indicating that flotillin-2 may be related to tumor metastasis.
In addition to flotillins, CD44, caveolin-1, mucin-1 (MUC1), and rat sarcoma (RAS) are also closely related to lipid rafts. CD44 is one of the principal cell adhesion receptors, and is involved in cancer cells migration, invasion and metastasis [5]. Proteolytic cleavage of CD44 plays a critical role in tumor cell migration, and is regulated by factors present in the tumor microenvironment, such as hyaluronan oligosaccharides and epidermal growth factors [6]. Murai T et al. reported that cholesterol depletion with methyl-β-cyclodextrin (MβCD), an agent used to disrupt lipid rafts, enhances CD44 shedding mediated by a disintegrin and metalloproteinase 10 (ADAM10) in human glioma and pancreatic cancer cells, and that cholesterol depletion also disorders CD44 localization to the lipid rafts. Simvastatin, a cholesterol-lowering medication, induced CD44 shedding, which prevented the induction of glioma cell migration by hyaluronan or epidermal growth factor (EGF) [7]. In a study by Yang ZS et al (Cav-1), cholesterol significantly inhibited the migration and invasion of HCC (hepatocellular carcinoma) cells. Of note, a high serum cholesterol level indicates a better prognosis in HCC patients [8]. High levels of cholesterol promote CD44 translocation into lipid rafts, and attenuate CD44-Ezrin binding, which are essential for cell migration and cancer metastasis. Therefore, targeting CD44-Ezrin signaling is a potential approach to improve the prognosis of HCC [8].

Caveolins are oligomeric structural proteins that are both necessary and sufficient for caveolae formation. The functions attributed to caveolae and Cav-1 are diverse, ranging from vesicular transport (transcytosis, endocytosis, and potocytosis) and cholesterol homeostasis, to the suppression of cell transformation and the regulation of signal transduction [9]. Cav-1 protects squamous epithelia by controlling cell growth and stabilizing cell junctions and matrix adhesion, and is regulated by cholesterol transcription via sterol-responsive element-binding protein-1 (SREBP1). Prade E et al. showed that bile acids down-regulated Cav-1 expression by inhibiting the proteolytic cleavage of a 125-kDa pre-SREBP1 from the endoplasmic reticulum/Golgi apparatus and preventing the nuclear translocation of active 68-kDa SREBP1. The disordered post-translational processing of SREBP1 impaired the transcriptional activation of SREBP1 response elements in the proximal human Cav-1 promoter. These data suggest that bile acid-mediated down-regulation of Cav-1 marks early changes in the squamous epithelium, which may lead to onset of Barrett’s esophagus (metaplasia) and the progression to Barrett’s adenocarcinoma (BAC) [10]. A high Cav-1 level is associated with drug resistance during the treatment of numerous cancers such as lung cancer, esophageal cancer, colorectal cancer and renal carcinoma [11-14]. Several biochemical compounds targeting Cav-1, such as chrysotobilenzyl, gigantol, moscatilin, cordycepin, Jorunnamycin A, albumin-encapsulated fenretinide and bleomycin exert anti-small-cell lung cancer (NSCLC) effects [15]. In a phase II trial, Bertino EM et al. evaluated carboplatin with nanoparticle albumin-bound (nab)-paclitaxel as first-line therapy for NSCLC, and reported that Cav-1 and secreted protein acid rich in cysteine (SPARC) expression in the tumor and stromal compartments could serve as prognostic and/or predictive biomarkers of NSCLC [16].

MUC1 is a type 1 transmembrane protein whose cytoplasmic tail acts as a scaffold for several signaling pathways. For patients with high-risk estrogen receptor positive (ER+) breast cancer, increased expression of the MUC1 glycoprotein is associated with resistance to anti-hormonal therapy, metastasis and death. The binding of MUC1 to ICAM-1 (intracellular adhesion molecule 1) can lead to the recruitment and activation of Src, and lipid raft microdomains play an important role in this promigratory signaling. MUC1 has unique structural characteristics, including that its transmembrane domain has both the length and hydrophobicity required for lipid raft residency [17]. Clinically, MUC1 expression is highly correlated with advanced disease, poor survival and tumor dissemination [18]. Inhibitors of the MUC1-C subunit have been developed that directly block its oncogenic function, and treatment with these inhibitors induces the death of breast cancer cells in vitro and in xenograft models [19]. It has been shown that the MUC1-Cytoplasmic Domain (MUC1-CD) accelerates the development of resistance to several therapeutic anticancer agents, including bortezomib, trastuzumab and tamoxifen [20]. Although it is still in preclinical and early clinical stage development, targeted treatments for MUC1 are under development, and seem to have great prospects for a number of tumor types, including lung cancer, pancreatic cancer and breast cancer [21].

Lysophosphatidic acid

Lipids are not only required for the synthesis of the cell membrane, they also support rapid cell division and produce a large number of molecules involved in signal transduction, such as phosphatidylinositol-3,4,5-triphosphate, ceramide-1-phosphate, lysophosphatidic acid (LPA), diacylglycerol and platelet-activating factor, which can promote tumor initiation and progression in humans [22].

LPA is a by-product of the lipid biosynthesis pathway that is expressed at a high level in several cancers and is associated growth-promoting activity. LPA is a prototypical ligand of the G protein-coupled receptor (GPCR) family, which have been reported to enhance the invasiveness of various tumors [23,24]. GPCRs also mediate a variety of other physiological and pathological functions related to oncogenesis. Several lysosphospholipids are activators of distinct GPCRs known to promote oncogenesis [22]. It has been shown that LPA can increase lipid synthesis by upregulating the SREBP1. SREBP1 is a key transcription factor that regulates lipid metabolism in cells, mainly by regulating the expression of the key enzymes required for
cholesterol and fatty acid synthetic processes [25]. It thereby regulates lipid synthesis and activates the SREBP-FAS and acetyl-CoA carboxylase (AMPK-ACC) cascade, leading to an increase in new lipid synthesis [26]. This effect of LPA can only be observed in malignant cells, while the LPA in non-transformed cells is unable to activate SREBP1, suggesting that tumor cells may activate SREBP1 through a specific mechanism. Because LPA can promote lipid synthesis by ovarian cancer cells, LPA has been considered as a pathogenic factor in the tumor microenvironment in these patients, but this effect remains to be confirmed in other tumors [22].

The tumor microenvironment

Tumor cells exhibit metabolic plasticity, which provides them survival and proliferation advantages under extreme conditions (such as hypoxia, acidosis, and malnutrition). In this microenvironment, the lipid synthesis of tumor cells increases, affecting the lipid metabolism of tumor cells [27]. A study on the role of the extracellular acidic environment in cancer progression confirmed that an acidic extracellular pH (pH = 6.8) triggered activation of SREBP2 by promoting its nuclear translocation and binding to its target promoters. When activated, SREBP2 can be used as a transport factor to bind the low-density lipoprotein (LDL) receptor or gene operons of HMGCoA synthetase (HMGCS), thus increasing the intracellular cholesterol level. Increasing evidence suggests that altered tumor metabolism and the accumulation of metabolites can lead to local immunosuppression in the tumor microenvironment [28]. A correlation analysis showed that there were differences in the expression of genes involved in lipid metabolism [i.e., HMGCS2, glutathione peroxidase 2 (GPX2), and CD36] associated with immunity, suggesting a potential interaction between lipid metabolism and the immune response [29].

The metabolic changes in the tumor microenviroment are considered as a hallmark of cancer, and provide new opportunities for treatment strategies used in conjunction with immune checkpoint therapy [30]. Research by Liu C et al. showed that Treg cells suppressed CD8+ T cell secretion of interferon-γ (IFNγ), which would otherwise block the activation of SREBP1-mediated fatty acid synthesis in immunosuppressive (M2-like) tumor-associated macrophages (TAMs) [31]. Of note, the pattern of lipid metabolism in macrophages can be changed by different factors in the tumor microenvironment. For example, upregulation of lipid oxidative is one of the metabolic characteristics of M2 macrophages activated by IL-4 [32]. The immunosuppressive phenotype of TAM is controlled by long-chain fatty acid metabolism (especially unsaturated fatty acids). Therefore, lipid droplets were identified as essential organelles, representing an effective target for chemical inhibitors to block the in vitro polarization of TAMs and inhibit tumor growth in vivo [33]. Abnormal lipid metabolism is also present in the myeloid-derived suppressor cells (MDSC), neutrophils and natural killer (NK) cells, which may contribute to tumor progression [34].

Proinflammatory cytokines associated with abnormal tumor lipid metabolism

In recent years, there has been increasing evidence that chronic inflammation is related to tumor transformation and progression, such as the transition to Barrett’s esophagus (BE) and subsequently to esophageal adenocarcinoma (EA), or may underlie the association between Helicobacter pylori infection and gastric cancer, inflammatory bowel disease and colorectal cancer, viral hepatitis and liver cancer, and so forth. During the process of tumorigenesis, the tumor microenvironment can induce the expression of a variety of proinflammatory cytokines, chemokines, and angiogenic factors by altering a number of different signaling pathways (such as activation of NF-κB, STAT3, AP-1, and others) to promote angiogenesis, tumor growth, invasion, and metastasis [35].

An increasing number of studies have reported an association between lipid metabolism and inflammatory reactions. Disordered lipid metabolism can enhance oxidative stress and affect the chronic inflammatory response. For example, LDL can promote the production of inflammatory mediators, such as interleukin-6 (IL-6) and tumor necrosis factor (TNF), and then aggravate the inflammatory reaction. In contrast, HDL plays an anti-inflammatory role by inhibiting the expression of endothelial cell adhesion molecules induced by cytokines and by reducing the chemotaxis of monocytes and lymphocytes [36].

In cancer patients with cachexia, the loss of adipose tissue occurs through lipolysis (mainly white adipose tissue), and the loss of muscle tissue usually occurs after significant changes in adipose tissue. Lipolysis results in an increase in the circulating free fatty acids (FFAs), which are absorbed by skeletal muscle. The excessive FFAs in muscle cells produce several biochemical changes, which eventually lead to skeletal muscle atrophy. In the environment of cancer cachexia, white adipose tissue browning is activated, and the light brown adipose tissue is significantly increased. This light brown adipose tissue plays the same function as brown adipose tissue, enhances heat production and promotes cancer cachexia [37] (Figure 2).

Changes in tumor cell lipid metabolism are important for the communication between tumor cells, and between the tumor cells and surrounding stromal and immune cells. Tumor cells use fatty acids to produce other bioactive lipids and mediators, which exert paracrine effects on other cells [38]. At the same time, in the inflammatory environment, adipose-derived tumor-supporting cells and macrophages secrete a series of proinflammatory cytokines and adipokines, leading to tumor cell growth and metastasis. Adipose tissue is also a source of cells that can alter the tumor microenvironment, including cancer-associated adipocytes (CAAs) that release
FFAs and inflammatory cytokines and adipose-derived stem cells (ACSs) that can contribute to the remodeling of the tumor microenvironment [39] (Figure 2).

Because proinflammatory cytokines like TNFα are often synthesized by activated macrophages, and these cells have been identified in the fat cells of cancer patients with weight loss, it is speculated that either (or both) immune cells or adipocytes may be the source of cellular factors involved in regulating energy pathways and lipid mobilization. In adipocytes, TNFα can inhibit the lipoprotein lipase activity and reduce triglyceride uptake and lipid deposition, leading to cachexia. Lu L et al. administered targeted therapy by coupling TNFα with TCP-1, a novel vascular-targeting peptide, in an orthotopic colorectal cancer model in mice. The combination of TCP-1/TNFα and 5-FU inhibited tumor growth, induced apoptosis, and reduced cell proliferation, revealing that TCP-1 could serve as a potential drug carrier for the treatment of colorectal cancer [40].

IL-6 is produced by activated macrophages and can induce an acute-phase reaction stimulated by the liver. Signal transduction via IL-6 is realized by the formation of a membrane binding receptor and heterodimer via signal transduction receptor (gp130) and activation of the JAK/STAT pathway[41]. It has been reported that the expression...

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**Figure 2** Mechanisms linking abnormal lipid metabolism to cancer and cancer-related cachexia.
of the interleukin 6 receptor is an independent prognostic factor for ovarian cancer, and may represent a potential therapeutic target [42]. Yousefi H et al. investigated the expression levels of IL-6 and the IL-6 receptor (IL-6R) in a panel of epithelial ovarian cancer (EOC) cell lines and found that the expression levels of IL6 and IL-6R were higher in therapy-resistant EOC cells compared to sensitive cells. The combination of tocilizumab, an anti-IL-6R monoclonal antibody, with carboplatin synergistically inhibited the growth and proliferation of EOC cells suggesting that blockade of the IL-6 signaling pathway with an anti-IL-6 receptor antibody like tocilizumab might resensitize the chemoresistant cells to treatment [43].

**Lipid metabolism-related enzymes**

Fatty acid synthesis is a complement cascade reaction of anabolism activated by adenosine triphosphate citrate lyase (ACLY), acetyl-CoA carboxylase (ACC) and fatty acid synthetase (FASN) [44]. ACLY catalyzes the conversion of citric acid to oxaloacetic acid and acetyl-CoA. It plays a role in tumors by activating the Akt signaling pathway, increasing enzyme levels and promoting metabolic activities [45]. ACLY is often overexpressed or overactivated in different types of cancers, including lung cancer, which is an important mechanism underlying the increase in lipid production via the de novo pathway in cancers. The E3 ubiquitin ligase cullin3 interacts with ACLY through its adaptor protein, KLHL25, and ubiquitinates and degrades ACLY. Thus, cullin3 reduces the level of acetyl-CoA and inhibits lipid synthesis by negatively regulating ACLY [46]. Elevated expression of ACLY in gastrin adenocarcinoma is related to advanced gastric cancer and lymph node metastasis [44].

ACC carboxylates acetyl-CoA to malonyl-CoA and has two isoforms, ACC1 and ACC2. ACC is the rate-limiting enzyme in the fatty acid synthesis pathway. Elevated expression of ACC1 correlates with several aggressive clinicopathological features of hepatocellular carcinoma (HCC), such as angioinvasion and poor differentiation [44].

FASN, a homodimeric protein, is another important rate-limiting enzyme in fatty acid synthesis. It uses glutamine and glucose as carbon sources to promote the de novo synthesis of long-chain fatty acid palmitate from acetyl-CoA and malonyl-CoA. The expression level of FASN in most normal human tissues is too low to be detected, but increased expression has been detected in transformed cells. Palmitate, the product of FASN, can change the biophysical properties of tumor cell membranes, and enables the micromembrane area to effectively assemble the signaling complexes needed for the sustained proliferation and survival of tumor cells [47]. FASN can regulate and integrate other carcinogenic signaling pathways, including the PKC, HER2, and PI3K/Akt/mTOR pathways [48]. High expression of FASN can be detected in breast, prostate, colorectal and other tumor tissue sections, and is related to the disease status [47].

**Dyslipidemia and solid tumors**

Endometrial cancer The morbidity of endometrial cancer ranks second among all gynecological malignancies and is still increasing in China [49]. Gong TT et al. conducted one cohort and nine case-control studies of the dose-response, and showed that the risk of endometrial cancer increased by 6% for every 100 mg/day increase in the dietary consumption of cholesterol, suggesting that there may be a positive association between dietary cholesterol consumption and the risk of endometrial cancer [50]. Nottingham University Hospital performed a cross-sectional study of a total of 102 women (34 participants each in the polycystic ovary syndrome, endometrial cancer and control groups). Clinical and biochemical assessments were performed before endometrial biopsies were obtained from all participants. The results showed that SREBP1 expression was significantly increased in the endometrium of women with polycystic ovary syndrome and women with endometrial cancer compared with controls, and its expression positively correlated with the serum triglyceride level in both groups[51].

Prostate cancer Normal prostate cells mainly generate energy through oxidative phosphorylation. However, during the processes of transformation, prostate cancer cells no longer secrete citrate and utilize the citric acid cycle, instead reactivating the Krebs cycle as a source of energy [52]. Obesity is a risk factor for prostate cancer, and it is associated with an increased incidence and recurrence rate of high-risk or aggressive prostate cancer [53]. Interventions to reduce obesity in high-risk populations is beneficial for the primary prevention of prostate cancer. Countries with higher dietary fat intake also have higher prostate cancer mortality.

The expression levels of ACLY, ACC and FASN are increased in prostate cancer cells [54]. About 70% of advanced prostate cancer cells have reduced expression of phosphatase and tensin homology deleted on chromosome ten (PTEN), which activates the PI3K pathway and promotes prostate cancer cell survival, metastasis and castration-resistant growth [55]. PTEN also participates in cholesterol ester storage [56]. As with several other cancers, SREBP1 is a key factor related to the progression of prostate cancer, and interference with related pathways may represent a strategy for treating prostate cancer [50].

Colorectal cancer is a common gastrointestinal cancer. There is evidence that abnormal lipid metabolism is closely related to the development and progression of colorectal cancer, with many studies showing that hyperlipidemia and obesity are major risk factors for colorectal cancer [57]. The lipid metabolism pathways affected in colorectal cancer cells include fatty acid synthesis, desaturation, elongation, and mitochondrial oxidation [58]. A high level of free fatty acids in serum may be related to oxidative stress and
increased lipotoxicity [59]. Recent evidence shows that colorectal cancer can reverse the Warburg effect, including fatty acid oxidation, which provides new insight into potential molecular therapeutic targets [60].

The available evidence indicates that there is a relationship between the expression of stearoyl CoA desaturase-1 (SCD-1) and various cancers. The overexpression of SCD-1, ATP binding cassette transporter A1 (ABCA1), long-chain acyl-CoA synthetase (ACSL1) and 1-acyl-sn-glycerol-3-phosphate acyltransferase α (AGPAT1) is associated with an increased risk of recurrence and a poorer prognosis in patients with stage II colon cancer [61]. There appears to be a relationship between cancer mortality and SCD-1 activity, as estimated by the serum cholesterol ester ratio (16:1 n-7 and 16:0), and based on the presence of single nucleotide polymorphisms in SCD-1 [62]. The endogenous synthesis of monounsaturated fatty acids may have an impact on cancer outcomes, indicating that SCD-1 may be a potential target of anti-cancer therapy [63]. The ACSL/SCD-1 pathway can regulate the invasiveness of cancer cells and serve as a predictor of survival and silencing SCD-1 with siRNA can induce apoptosis in HCT116 cells [64].

Dyslipidemia is a risk factor for the occurrence and metastasis of endometrial cancer, prostate cancer, and colorectal cancer, among others. However, the mechanism(s) by which dyslipidemia affects the occurrence and metastasis are still being elucidated, so more in-depth research is needed.

Conclusions

Metabolic reprogramming is an important process that both leads to and results from cellular transformation. Studies have shown that abnormal lipid metabolism is closely related to the occurrence and development of tumors. Lipids affect the functions of the cell membrane and regulate energy metabolism. Lipid rafts are closely related to the signal transduction and protein sorting of the membrane, and participate in the occurrence, development and metastasis of tumors by regulating the lipid metabolism of some tumors. Further studies are needed to identify the regulatory mechanisms, such as the full pathways regulating the expression of lipid metabolism-related genes, because this would help to identify new targets for tumor prevention and therapy.

Because inflammatory factor-mediated chronic inflammation plays a key role in tumor progression, the development of anti-tumor drugs targeting inflammatory factors such as TNFα and IL-6 has become a hot area of research. However, the clinical application has so far been limited due to issues with cytotoxicity, so more research is needed. Abnormal lipid metabolism in tumor cells is mainly manifested in uncontrolled de novo synthesis of fatty acids and enhanced lipid synthesis, which permit the continuous proliferation of tumor cells. These changes are closely related to the enzymes involved in lipid synthesis. Therefore, ACLY, ACC and FASN are potential therapeutic targets, which may have broad applications in anti-cancer therapy. It will be helpful to have a deeper understanding of the mechanisms of tumorigenesis and progression and the regulation of tumor liposynthesis-related enzymes. Such information will be useful to help prevent the development of tumors or halt their progression.

Abbreviations

TME, tumor microenvironment; CAAs, cancer-associated adipocytes; ASCs, adipose-derived stem cells; FFAs, free fatty acids; Fas, fatty acids; MMPs, matrix metalloproteinase; IL, interleukin; SDF-1, stromal-derived factor-1; TGF-β, transforming growth factor β; TNFα, tumor necrosis factor α; VEGF, vascular endothelial growth factor; TAMs, tumor-associated macrophages; PGE2, Prostaglandin E2; NK cells, natural killer cells; Treg cells, regulatory T cell; TAN, tumor-associated neutrophil; UCP1, uncoupling protein 1.

Conflict of interest

The authors declare that there is no conflict of interest.

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