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EDITORIAL

Dysregulated lipid metabolism in cancer

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Abstract

Alteration of lipid metabolism has been increasingly recognized as a hallmark of cancer cells. The changes of expression and activity of lipid metabolizing enzymes are directly regulated by the activity of oncogenic signals. The dependence of tumor cells on the dysregulated lipid metabolism suggests that proteins involved in this process are excellent chemotherapeutic targets for cancer treatment. There are currently several drugs under development or in clinical trials that are based on specifically targeting the altered lipid metabolic pathways in cancer cells. Further understanding of dysregulated lipid metabolism and its associated signaling pathways will help us to better design efficient cancer therapeutic strategy.

Key words: Lipid metabolism; Lipogenesis; Fatty acid oxidation; Cancer

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INTRODUCTION

Cancer cells reprogram their metabolic pathways to meet their abnormal demands for proliferation and survival[1,2]. It has long been recognized that cancer cells need a higher rate of metabolism to support their accelerated proliferation rate[1,2]. The most known metabolic change is a phenomenon called "Warburg effect" first described by Otto Warburg in 1920s. He reported that cancer cells take up and utilize much more glucose for glycolysis compared to normal cells, even in the normoxic condition[3]. It has been recently proposed that aerobic glycolysis is the core cellular metabolism to provide cancer cells with not only energy but also the building blocks for macromolecule synthesis, such as carbohydrates, proteins, lipids and nucleic acids[4]. In the last decade, the altered lipid metabolism has increasingly been recognized as another common properties of malignant cells[2,5]. Like glucose metabolism, lipid metabolism in cancer cells is also regulated by the common oncogenic signaling pathways, and is believed to be important for the initiation and progression of tumors[5]. A number of lipogenic enzymes utilize reduced nicotinamide adenine dinucleotide phosphate (NADPH) and acetyl-CoA generated from glucose and glutamine metabolism, to synthesize fatty acids and their derivatives. Therefore, the exacerbated lipogenesis in cancer cells is not only caused by the upregulation of lipid metabolizing enzymes, but is also directly coupled to other common metabolic pathways and their associated cell signaling pathways[1,2] (Figure 1).

ALTERED LIPID METABOLISM IS IMPORTANT FOR THE PATHOGENESIS OF CANCER

Malignant transformation alters both biosynthetic and bioenergetic requirements for cancer cells. Continuous *de novo* lipogenesis provides cancer cells with membrane building blocks, signaling lipid molecules, posttranslational modifications of proteins as well as energy supply to support rapid cell proliferation (Figure 2). First, quite a number of endogenously synthesized fatty acids are esterified to phospholipids, which provide pivotal structural lipids, facilitate the formation of detergent-resistant membrane microdomain for signal transduction, intracellular trafficking, polarization, and migration required for cancer cells[5-7]. Second, the newly generated lipids molecules, such as phosphatidic acid (PA), diacylglycerol (DAG), and lysophosphatidic acid (LPA), also mediate signal transduction in cancer cells[5-7]. These lipids regulate a variety of cellular functions including cell proliferation, survival and migration by either activating other signaling proteins inside the cells, or binding to a series of G protein-coupled receptors (GPCRs) on the cell surfaces. Third, the post-translational protein modification with lipid is also a vital process in regulating expression, localization and function of various signaling proteins. Phosphatidylinositol (PI)-associated modification through a carbohydrate linker to the proteins (GPI-anchored proteins) directs them toward to cell surface from endoplasmic reticulum (ER)[8]. Some GPI-anchored proteins, such as urokinase-type plasminogen activator (uPA)-receptor (uPAR) and membrane anchored serine protease matriptase (also known as MT-SP1 and epithin), have strong association with cancer[9,10]. The lipid covalent modification of Hedgehog and Wnt, two important signal molecules, regulates their signaling capacity and secretion[11-13]. The Ras small GTPase family members are also regulated by their prenylation status. The lipidation controls the trafficking of Ras GTPases among ER, Golgi and plasma membranes and determines the signaling outputs[14-16]. Finally, in response to glucose limitation, fatty acid can also be consumed through β-oxidation to provide key substitute energy for cancer cell survival. It is reported that stimulation of fatty acid oxidation is sufficient to maintain cell survival and protect cells from glucose withdrawal-induced death in Akt-overexpressing glioblastoma[17]. In some types of cancers, such as prostate cancer, fatty acid oxidation is proposed to be a dominant bioenergetic pathway[18].

DYSREGULATION OF LIPID METABOLIZING ENZYMES IN CANCER CELLS

Living cells acquire fatty acids for their metabolic demand from two major sources, exogenous dietary and *de novo* endogenous synthesis. Proliferative embryogenic cells actively use *de novo* synthesized fatty acids, whereas most adult normal cells preferentially use exogenous fatty acids. Interestingly, similar to embryonic cells, breast cancer cells (and many other types of cancer cells) endogenously synthesize 95% of fatty acids, despite how abundant the extracellular fatty acids are[19]. Moreover, cancer cells seem to be highly dependent on *de novo* lipogenesis for their proliferation and survival[1,5]. The expression and activity of many enzymes involved in fatty acid synthesis, *i.e.*, ATP citrate lyase (ACL), acetyl-CoA carboxylase (ACC) and fatty acid synthase (FASN), are upregulated in many types of cancers[1,5]. It is likely that the newly synthesized fatty acids are different in compositions compared to the circulating fatty acids and some cellular lipid pools require the *de novo* synthesized fatty acids. It has been well recognized that the upregulation of the fatty acid biosynthetic pathway starts at a relatively early stage in various types of tumors[5,20].

ACL converts cytosolic citrate to acetyl-CoA and oxaloacetate (OAA). Inhibition of ACL by small interfering RNAs (siRNAs) or the chemical inhibitor SB-204990 limits proliferation and survival of tumor cells *in vitro* and reduces tumor growth *in vivo*[21]. ACL activity is much higher in human lung adenocarcinoma compared to normal lung tissue and is well associated with the differentiation grades and a poorer prognosis[22]. ACC carboxylates acetyl-CoA to produce malonyl-CoA, a key intermediate in fatty acid synthesis that also serves as an allosteric inhibitor of fatty acid oxidation. The malonyl-CoA is further converted by FASN to long-chain fatty acids. Silencing of FASN or ACC-α by siRNAs in breast cancer cells results in a major decrease in palmitic acid synthesis. Supplementation of the culture medium with palmitate completely rescues cells from apoptosis induced by ACC-α and FASN knockdown, indicating the importance of lipogenesis in cancer cell survival[23]. Increased FASN is obviously correlated with a higher risk of recurrence and poor prognosis in human breast carcinoma patients[24]. Specific inhibition of FASN gene by siRNA leads to apoptosis of prostate tumor cells[25]. Overexpression of FASN induces invasive adenocarcinomas in human prostate epithelial cells and protects cells from apoptosis. In human prostate cancer specimens, FASN expression is inversely associated with the apoptotic rate[26]. Exacerbated endogenous fatty acid biosynthesis induced by FASN overexpression in non-cancerous epithelial cells is sufficient to cause a cancer-like phenotype[19]. Increased FASN has also been linked to short-term survival in colorectal and ovarian cancers[27]. Elevated expression and activity of FASN is one of the early events in the development and progression of lung squamous cell cancer[20], prostate cancer[28] and melanoma[29]. Furthermore, the high FASN expression leads to an overall high proliferative index in prostate cancer[28] and the intensity of FASN expression is related to prognosis in melanoma[29]. Pharmacological inhibition of fatty acid synthesis is reported to be selectively cytotoxic to cancer cells *in vivo* and *in vitro*[30,31]. Taken together, these evidences strongly support that *de novo* lipogenesis has a significant contribution to tumor

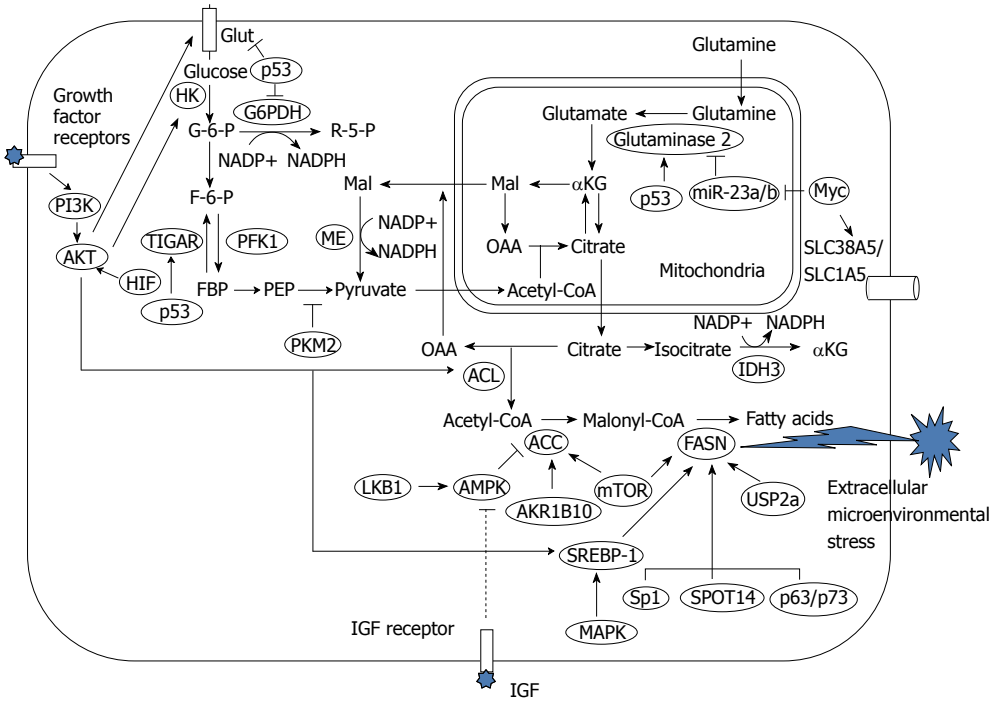

Figure 1 Signaling pathways regulating lipogenesis in cancer cells. This scheme represents the main regulation of lipogenesis in cancer cells. Lipid metabolizing enzymes are regulated by oncogenic signals. Growth factor-activated PI3K-AKT or hypoxia-induced HIF stimulates glucose transporters and hexokinases to promote glycolysis, providing more synthetic precursors for fatty acid synthesis. Akt also activates the lipogenic enzyme activity and expression through direct phosphorylation or SREBP-mediated transcription enhancement of lipogenic genes. The tumor suppressor, p53, plays a role in glucose uptake, pentose phosphate pathway and anaplerosis of citrate. As a transcription factor, p53 also enhances the expression of glucose transporters and Glutaminase 2. The inductive effect on TIGAR and the activity inhibition of G6PDH caused by catalytic effect of p53 constitute a complex regulation on pentose phosphate pathway imposed by p53. LKB1/AMPK pathway, the master regulator in cellular energetic metabolism, modulates ACC activity either by direct phosphorylation or through SREBP-1. Myc is involved in lipid metabolism and promotes citrate anaplerosis through increasing glutamine transporters and glutaminase 2 expression. The activity and expression of lipogenic enzyme, ACL, ACC and FASN, are regulated at multiple levels through mTOR, MAPK, USP2a, Sp1, *etc.* Glut: Glucose transporter; HK: Hexokinase; G-6-P: Glucose-6-phosphate; F-6-P: Fructose-6-phosphate; FBP: Fructose-1,6-bisphosphate; GFR: Growth factors receptor; PI3K: Phosphatidylinositol 3-kinase; MAPK: Mitogen activated protein kinase; SREBP-1: Sterol-regulatory element-binding protein-1; TIGAR: TP53-induced glycolysis and apoptosis regulator; OAA: Oxaloacetate; ACL: ATP citrate lyase; ACC: Acetyl-CoA carboxylase; FASN: Fatty acid synthase; FA: Fatty acids; G6PDH: Glucose-6-phosphate dehydrogenase; αKG: α-ketoglutarate; PFK: Phosphofructokinase; NADPH: Nicotinamide adenine dinucleotide phosphate; Mal: Malate; ME: Malic enzyme; Ac-CoA: Acetyl-CoA; mTOR: Mammalian target of rapamycin; USP2a: Ubiquitin-specific protease-2a; IDH3: Isocitrate dehydrogenase 3; R-5-P: Ribose-5-phosphate; HIF: Hypoxia-inducible factor; EMS: Extracellular microenvironmental stress.

pathogenesis.

The increased fatty acid synthesis has been long proposed to lead to the upregulation of phospholipid synthesis that fits the need of membrane biogenesis in highly proliferative cancer cells. However, very few studies have experimentally demonstrated the direct connection between fatty acid and phospholipid syntheses in cancer cells. One of the reasons might be the lack of a relatively simple method that allows investigators to analyze the very complex phospholipids. A recent mass spectrometry-based phospholipid analysis revealed that the tumor tissues with increased FASN expression displayed a consistent increase in saturated and mono-unsaturated acyl chains and a decrease in polyunsaturated species compared with normal tissues[32]. Inhibition of enzymes involved in fatty acid synthesis by the small molecule inhibitor soraphen A and siRNAs markedly decreases the saturated and mono-unsaturated phospholipid species. The more saturated acyl chains appear to protect cancer cells from oxidative stress- and doxorubicin-induced cell death[32]. In another global phospholipid analysis of breast cancer tissues, the increase of a saturated phosphatidylcholine (14:0/16:0) is also found to correlate with the aggressiveness of breast cancer[33].

To date, the majority of research on cancer lipid metabolism has focused on the increase of fatty acid synthesis. Interestingly, lipolytic remodeling of lipid species has also recently been reported to promote the tumorigenic properties of cancer cells[34]. Using a functional screen, the activity of a lipolytic enzyme, monoacylglycerol lipase (MAGL), was unexpectedly found to be highly elevated in aggressive cancer cells from multiple tissues of origin. MAGL hydrolyzes monoacylglycerols (MAGs) to release glycerol and a free fatty acid. Furthermore, the more aggressive cancer cell lines and high grade primary tumors contain increased free fatty acid levels, which could be reduced by the MAGL inhibitor JZL184 and short hairpin RNAs, suggesting MAGL-dependent lipolysis is a major source of intracellular free fatty acids. The MAGL-regulated lipid hydrolysis appears to be important for the transformed properties of tumor cells. Inhibition of MAGL inhibits migration, invasion and survival of cancer cells *in vitro* and xenograft tumor growth in mice. Strikingly, the functional defects of MAGL inhibition

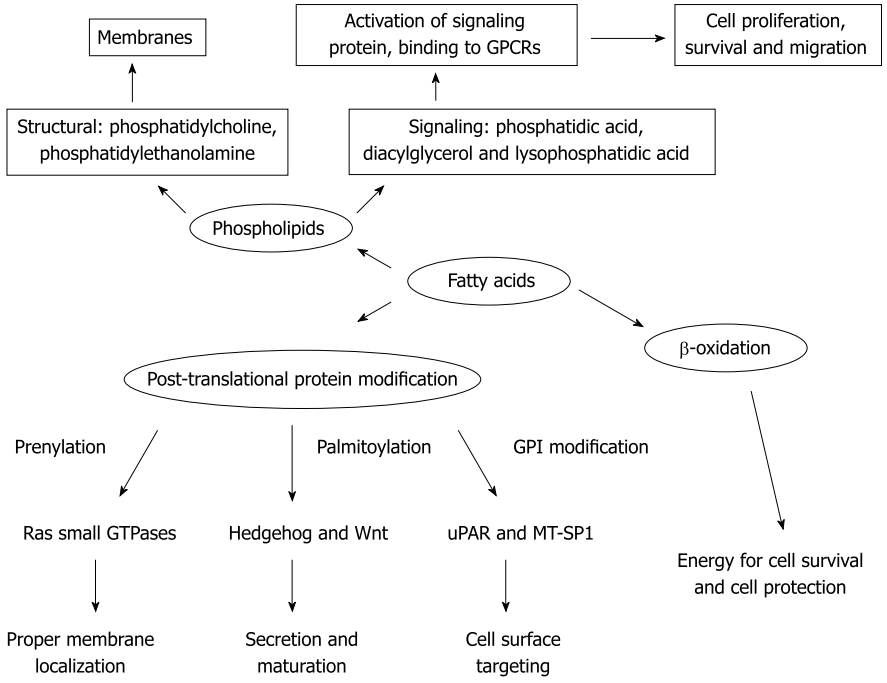

Figure 2 The functions of lipids in cancer cells. Lipids provide cancer cells with membrane building blocks, signaling molecules, posttranslational modifications of proteins and energy supply to support rapid cell proliferation. GPCRs: G protein-coupled receptors; uPAR: Urokinase-type plasminogen activator-receptor.

were reversed by exogenous addition of saturated fatty acids *in vitro* or feeding mice a high-fat diet. Finally, the authors demonstrated that the production of signaling lipids, such as PA, LPA, and prostaglandin E2 (PGE_2), mediates at least part of the oncogenic properties of MAGL. The question raised from this study is why both lipogenesis and lipolysis are increased in cancer cells. Further studies need to be performed to test whether fatty acids derived from *de novo* synthesis versus lipolytic release differ in both compositions and functions.

THE DYSREGULATED LIPID METABOLISM IN CANCER CELLS IS REGULATED BY ONCOGENIC SIGNALS

The alteration of lipid metabolism in cancer is downstream of many known oncogenes and tumor suppressors, such EGFR, phosphatidylinositol 3-kinase (PI3K), MAPK, Myc, p53[1,5]. In addition to their recognized roles in regulating cell proliferation and survival, these oncogenic signals also promote the expression and activity of enzymes involved in fatty acid synthesis. It has been reported that oncogenic signaling pathways regulate lipid metabolism at multiple steps, including transcriptional, translational and post-translational levels. FASN and ACC are used here as two examples to depict the complexity of oncogenic signal regulation of lipid metabolizing enzymes. The major controller of FASN expression in tumor cells is growth factor receptor-associated signaling pathways, including the PI3K-Akt pathway and the mitogen-activated protein kinase (MAPK) pathway[35,36]. PI3K-Akt and MAPK pathways regulate FASN expression through the sterol regulatory element-binding protein-1 (SREBP-1) transcription factor, which is the master regulator of fatty acid metabolism[35,37]. Sp1, a transcription factor of the Sp/KLF family, regulates FASN expression in colon and prostate cancer cells through interacting with Sp1 binding sites in FASN promoter[38]. Recent reports show that FASN expression is also modulated by other transcription factors, such as the members of p53 family and the lipogenesis-related nuclear protein SPOT14[39,40]. Furthermore, posttranslational regulation also contributes to the regulation of FASN expression in cancer cells. In prostate cancer, the isopeptidase ubiquitin-specific protease-2a (USP2a) has been found to interact with and stabilize FASN protein through removing ubiquitins from FASN. Functional inactivation of USP2a results in reduced FASN protein expression and decreased cell proliferation and enhanced apoptosis[41]. In prostate adenocarcinoma, the significant gain in FASN gene copy number is supposed to cause the resultant increase in FASN protein expression[42].

In addition to the intracellular signaling pathways, FASN expression is also affected by extracellular microenvironmental stresses. The hostile microenvironment of solid tumors, such as hypoxia, low pH, and nutrient starvation could activate several intracellular signaling pathways to promote FASN expression[36]. Hypoxia induces FASN expression through the activation of Akt and HIF1 followed by the induction of SREBP-1 gene[43]. In addition, extracellular acidosis can upregulate the transcriptional expression of FASN gene in breast cancer cells via an epigenetic fashion[44].

In HER2-overexpressing breast cancer cells, such as BT-474 and SK-BR-3 cells, the increased expres-

sion of FASN and ACCα proteins are not mediated by SREBP-1, but is regulated via the activation of the PI3K-mTOR signaling pathway at translational level[45]. The best known regulator of ACC is AMPK. AMPK phosphorylates and inactivates ACC *in vitro* and *in vivo*[46,47]. In human lung adenocarcinoma, the expression patterns and levels of LKB1 and phospho-ACC are relevant, suggesting ACC activity is regulated through LKB1-AMPK pathway[48]. In colon cancer cells, IGF-1 reduces ACCα phosphorylation via an ATM/AMPK signaling pathway whereas suppresses ACCα expression through an ERK1/2-dependent signaling pathway[49]. The protein level of ACCα is also determined by its interaction with aldo-keto reductase family 1 member B10 (AKR1B10), which associates with ACCα and blocks its ubiquitination and proteasome degradation[50].

LIPOGENESIS IS DIRECTLY COUPLED TO GLUCOSE AND GLUTAMINE METABOLISM IN CANCER CELLS

De novo lipid biosynthesis is directly supported by the generation of acetyl-CoA and NADPH from glucose and glutamine metabolism, which is regulated by a number of oncoproteins and tumor suppressors. Glycolysis provides the carbon source, acetyl-CoA, for the *de novo* fatty acid synthesis. During aerobic glycolysis, glucose is broken down to pyruvate. A series of enzymes are involved in the glycolytic reaction and considered to be highly relevant to tumorigenesis, such as glucose transporter 1 (GLUT1), hexokinase (HK), pyruvate kinase (PK)[51,52]. Glucose-derived pyruvate sequentially enters the mitochondria and is decarboxylated to acetyl-CoA by pyruvate dehydrogenase (PDH), an enzyme located in the inner mitochondrial membrane. OAA in mitochondria condenses with glucose-derived acetyl-CoA to form citrate through TCA cycle. A part of citrate generated from the TCA cycle exits mitochondria and is catalyzed by ACL to cytosolic acetyl-CoA, as the precursor of fatty acids biosynthesis[53]. Akt regulates the level of acetyl-CoA by directly phosphorylating and activating ACL[54]. To maintain TCA cycle, the citrate exported to cytosol from mitochondria must be replenished. The recurrence of citrate is through glutaminolysis. p53 enhances the expression of glutaminase-2, which catalyzes glutamine to glutamate in mitochondria, to promote citrate regeneration[55]. Glutaminase-2 mRNA is induced in HCT116, MCF-7, and U2OS by oxidative genotoxic damage treatment that activates p53 and protects cells from ROS-sensitive apoptosis[56]. Myc also plays critical role in glutamine metabolism. It promotes glutaminolysis and triggers cellular addiction to glutamine by direct and indirect transcriptional regulation of genes involved in glutamine metabolism. On one hand, Myc binds to the promoters and induces the expression of SLC38A5 and SLC1A5, two high affinity glutamine transporters, to promote cellular glutaminolysis[57,58]. Suppression of Myc expression using small hairpin RNAs in human SF188 glioma cells leads to a significant reduction in glutaminolysis, indicated by glutamine consumption and ammonia production[58]. On the other hand, Myc represses the transcription of miR-23a and miR-23b, leading to greater expression of their target protein, mitochondrial glutaminase, in human P-493 B lymphoma cells and PC3 prostate cancer cells[59], therefore, enhancing cancer cell glutaminolysis indirectly. Moreover, Myc-stimulated mitochondrial glutamine metabolism results in a decreased contribution of glucose to the mitochondrial-dependent synthesis of phospholipids[57].

NADPH is another essential component required for fatty acid biosynthesis. Large amounts of NADPH are consumed during *de novo* lipid synthesis. Enhanced lipogenesis in cancer cells has also been proposed to be required to balance the redox potential through the use of NADP oxidase[60]. There are several manners to generate NADPH in living cells. The predominant one is through the pentose phosphate pathway (PPP). In PPP, glucose-6-phosphate is diverted from the glycolytic pathway to generate pentose sugars and NADPH[61]. Glucose-6-phosphate dehydrogenase (G6PDH), which is the rate-limiting step in the oxidative pentose phosphate pathway (ox-PPP), is involved in NADPH production[62]. Recently, it was demonstrated that p53 inhibits the entry point to the PPP by direct intervention of G6PDH activity. The inhibition effect of p53 is independent of its transcriptional activity and is through directly controlling the enzymatic activity of G6PDH[63]. The deficiency of p53 results in a significant increase in NADPH level in HCT116 and U2OS cells[63]. The flux of PPP is also affected by another p53 target protein, known as TIGAR (TP53-induced glycolysis and apoptosis regulator), an enzyme that dephosphorylates fructose-2,6-bisphosphate (FBPs) to fructose-6-phosphate. The activity of TIGAR counteracts that of phosphofructokinase (PFK), a key regulatory enzyme in glycolysis. Thus, activation of TIGAR supports the shuttling of glucose-6-phosphate into PPP instead of ongoing glycolysis, to produce more NADPH for biosynthesis[64]. Significant induction of TIGAR mRNA was observed in U2OS and RKO cells after treatment with actinomycin D, a p53 agonist[64]. In addition, PPP is regulated by pyruvate kinase isoform M2 (PKM2), which is predominantly expressed in self-renewing cells such as embryonic and adult stem cells and tumor cells[65]. PKM2 controls the conversion of phosphoenolpyruvate (PEP) to pyruvate, the rate-limiting step of glycolysis. PKM2 promotes PPP by inhibiting glycolysis and slowing the passage of metabolites through glycolysis, so that these substrates can be shuttled into other subsidiary pathways such as PPP to generate more NADPH. Knockdown of PKM2 expression in human cancer cell lines and replacing it with PKM1 reduced tumor formation in nude mouse xenografts, correlated with the decreased lactate production and increased oxygen consumption[66]. Apart from PPP, some other pathways are also involved in NADPH generation in proliferative cells. Citrate derived from TCA cycle can be exported to cytosol and generate NADPH through two independent pathways. One reaction converts citrate to α-ketoglutarate

(α-KG) through isocitrate, which is catalyzed by NADP-dependent isocitrate dehydrogenase 1 (IDH1). IDH1 is structurally and functionally distinct from the NAD-dependent enzyme IDH3, which functions in the TCA cycle to produce NADH that is consumed for oxidative phosphorylation. The gain of function mutations of IDH1 were found in a high frequency in adult grade Ⅱ and grade Ⅲ gliomas and acute myeloid leukemia (AML)[2]. Another reaction related to NADPH production from citrate is through malate conversion. OAA derived from cytosolic citrate is catalyzed to malate, which is converted to pyruvate by malic enzyme concurrently generating NADPH. Malate circulating in TCA cycle can also be exported to cytosol directly to participate in NADPH production. In both routes, malic enzyme is necessary for NADPH generation. Therefore, malic enzyme is considered to be a lipogenic enzyme whose activity correlates with *de novo* fatty acid synthesis[67] and is found to be highly expressed in tumor cells[68].

LIPID METABOLISM AS TARGETS FOR CANCER THERAPY

Many enzymes involved in lipid metabolism are selectively overexpressed in cancer cells, making them good targets for cancer therapy. Indeed, a variety of agents have been developed to target lipogenic enzymes and the key regulators involved in lipid metabolism in cancer cell for therapeutic purpose. One of the most attractive targets for inhibition in cancer chemotherapy is FASN, due to its high degree of overexpression in cancer cells. The development of several FASN inhibitors have been reported from both academic labs and industries, such as Cerulenin, C75, orlistat, C93, C247, and GSK837149A[69]. When used in *in vitro*, xenograft and genetically induced mouse model studies, these inhibitors have supported FASN as an excellent target[1,69]. They killed cancer directly or sensitized them to other therapies such as 5-fluorouracil and trastuzumab[70-73]. A potential negative aspect of FASN inhibition might be its effect on food intake and body weight. Mice treated with cerulenin and C75 exhibited decreasing eating and consequent rapid weight loss, which may be caused by the inhibition of carnitine palmitoyltransferase 1 (CPT-1) in the hypothalamus[74-76].

In addition to FASN, other lipogenic enzymes are also promising targets for cancer therapy. Stable knockdown of ACL by RNAi significantly impairs glucose-dependent lipid synthesis and decreases cytokine-stimulated cell proliferation *in vitro* and prevents Akt-mediated tumorigenesis *in vivo*[53]. Selective inhibition of ACL by chemical inhibitor SB-204990 limits proliferation and survival of tumor cells *in vitro* and *in vivo*[21,22]. Knockdown the expression of ACC-α by RNAi leads to inhibition of cell proliferation and induction of caspase-mediated apoptosis in highly lipogenic LNCaP prostate cancer cells[77]. In preclinical studies, 6-amino-nicotinamide (6-An) that inhibits G6PDH, have demonstrated anti-tumorigenic effects in leukemia, glioblastoma and lung cancer cell lines[78]. Furthermore, targeting fatty acid oxidation also appears to be promising. Inhibition of CPT-1 by shRNA or its inhibitor etomoxir sensitizes human leukemia cells to chemotherapy[79]. Additionally, MAGL inhibitors suppress the pathogenesis of aggressive cancer cells[34].

CONCLUSION

There are increasing evidences to support that oncoproteins directly reprogram the metabolism of cancer cells, and make them addict to certain metabolic pathways. Therefore, the signaling pathways controlling the altered metabolism in cancer cells are attractive targets for cancer therapy. Like the Warburg effect, alteration of lipid metabolism is another nearly ubiquitous change in tumor cells. However, there is a lack of clear understanding of lipid metabolism in cancer cells. The increased *de novo* lipogenesis in cancer cells has been well described. Interestingly, recent studies also reported that lipolysis and lipid oxidation are upregulated in cancer cells[18,31,34]. In fact, fatty acid oxidation is a dominant bioenergetic pathway in prostate cancer cells[18]. It is still unclear why both lipid biosynthetic and mobilizing activities are upregulated in cancer cells. Further investigation on the regulation of these pathways will offer new therapeutic opportunities for the development of anticancer agents. Meanwhile, these tumor-associated lipid metabolism features may be used in the diagnosis and prognosis of human cancers.

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