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Cellular Fatty Acid Metabolism and Cancer

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Abstract

Cancer cells commonly have characteristic changes in metabolism. Cellular proliferation, a common feature of all cancers, requires fatty acids for synthesis of membranes and signaling molecules. Here, we provide a view of cancer cell metabolism from a lipid perspective, and we summarize evidence that limiting fatty acid availability can control cancer cell proliferation.

Introduction

Although cancers are hugely diverse in type and etiology, cancer cells frequently share the attribute of metabolic abnormalities. For example, glucose metabolism is commonly altered to decouple glycolysis from pyruvate oxidation (the Warburg effect) so that carbohydrates are not used for maximal ATP generation via mitochondrial respiration, despite high oxygen availability. A better understanding of these metabolic changes has prompted new approaches toward cancer therapy (reviewed in Hsu and Sabatini, 2008; Schulze and Harris, 2012).

Alterations in fatty acid (FA) metabolism in cancer cells have received less attention but are increasingly being recognized. FAs consist of a terminal carboxyl group and a hydrocarbon chain, mostly occurring in even numbers of carbons, that can be either saturated or unsaturated. They are required for energy storage, membrane proliferation, and the generation of signaling molecules. Here, we provide a brief review of metabolism in cancer cells, focusing on pathways of FA synthesis and storage. Furthermore, we examine a model for attenuating cancer cell proliferation and metastasis by manipulating FA metabolism to diminish FA availability. Due to the great diversity of cancer cells, our perspective is meant

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to be provocative, not universal. Nevertheless, our intention is to provide a framework for the generation of new ideas on how to manipulate fatty acid metabolism in cancer cells.

Alterations in Energy Metabolism in Cancer Cells

Cancer is fundamentally a disorder of cell growth and proliferation, which requires cellular building blocks, such as nucleic acids, proteins, and lipids. Cancer cells often have perturbed metabolism that allows them to accumulate metabolic intermediates as sources of these building blocks.

The most understood metabolic perturbation in cancer cells is the Warburg effect, an energetically wasteful alteration to glucose metabolism in which cancer cells use carbon from glucose to build other molecules instead of completely oxidizing them to carbon dioxide (Warburg, 1956). During normal cellular metabolism in the presence of oxygen, glucose undergoes glycolysis in the cytoplasm to produce pyruvate. After import into mitochondria, pyruvate is oxidized to acetyl-CoA, which then enters the Krebs cycle to produce reducing equivalents for oxidative phosphorylation (Figure 1). When oxygen is limiting, excess pyruvate is fermented to lactate in the cytoplasm. Differentiated cells typically use oxidative phosphorylation because of its efficiency, with one glucose molecule undergoing complete oxidation to yield ~36 ATP molecules versus 2 ATP that are obtained from anaerobic glycolysis. The Warburg effect is the use of fermentation even in the presence of oxygen and is characterized by an increase in glucose uptake and consumption, a decrease in oxidative phosphorylation, and the production of lactate[1].

Another commonly observed metabolic alteration in cancer is increased glutamine metabolism. In mammalian cells, glutamine is a major energy substrate through its metabolism to produce α-ketoglutarate, which feeds into the Krebs cycle. Glutamine-derived α-ketoglutarate contributes to the production of citrate by forward-flux through the Krebs cycle and malic enzyme-dependent production of pyruvate (DeBerardinis et al., 2007). Glutamine can also be converted to citrate by the reversal of the Krebs cycle reactions catalyzed by isocitrate dehydrogenase and aconitase (Wise et al., 2008; Mullen et al., 2012; Metallo et al., 2012). Citrate can then be used for the production of acetyl-groups for FA synthesis (see below).

Lipid metabolism is also altered in rapidly proliferating cells (for general reviews, see Swinnen et al., 2006; DeBerardinis and Thompson, 2012; Santos and Schulze, 2012). Here we focus on cancer and FA metabolism. In cancer cells, carbon must be diverted from energy production to FAs for biosynthesis of membranes and signaling molecules. The bulk of cell membrane lipids are phospholipids (PLs), such as phosphatidylcholine (PC) and phosphatidylethanolamine (PE), in addition to other lipids, such as sterols, sphingolipids, and lyso-PLs. All of these lipids are derived in part from acetyl CoA, and many contain FAs. The FA building blocks come from either exogenous sources or from *de novo* FA synthesis. While most normal human cells prefer exogenous sources, tumors synthesize FA *de novo* (Medes et al., 1953) and often exhibit a shift toward FA synthesis (Ookhtens et al., 1984). To enter the bioactive pool, FAs require “activation” by covalent modification by CoA via fatty acyl CoA synthetases. Once in the active pool, FAs can be esterified with glycerol or sterol backbones, generating triacylglycerols (TGs) or sterol esters (SEs), respectively, and then stored in lipid droplets (LDs) (See Figure 1). Within cells, FAs can have many fates, including being incorporated into membrane, storage, or signaling lipids, or oxidized to carbon dioxide as an energy source.

Although this review focuses on *de novo* FA synthesis pathways, some tumors scavenge lipids from their environment, rendering FA uptake pathways as a potential target. For example, fatty acid binding protein 4 (FABP4), a lipid chaperone, is implicated in providing

FAs from surrounding adipocytes for ovarian tumors (Nieman et al., 2011). Also, prostate cancer cells show reduced viability in the presence of FASN (C75) or ACLY (SB-204990) inhibitors only when cultured in the absence of lipoproteins, an exogenous lipid source (Ros et al., 2012). CD36, a widely expressed transmembrane protein with diverse functions that include fatty acid uptake, has been implicated in breast cancer, and decreased levels of CD36 in stromal tissue are correlated with early steps in tumorigenesis (Defilippis et al., 2012). It is noteworthy that *in vitro* conditions for cell culture experiments are likely to be different than *in vivo* conditions, where exogenous uptake may be more important in some cancers.

Limiting Supplies of Fatty Acids to Limit Cancer Cell Proliferation

Since FAs are essential for cancer cell proliferation, limiting their availability could provide a therapeutic strategy. From the perspective of lipid metabolism, limiting FA availability could be achieved in several ways: 1) blocking FA synthesis, 2) increasing FA degradation via oxidation, 3) diverting FAs to storage, or 4) decreasing FA release from storage (Figure 2). Limiting FAs through these mechanisms could be accomplished in isolation or in a combinatorial manner. Using this as a framework, we review evidence relevant to this model.

Blocking Fatty Acid Synthesis

The simplest way to reduce FA levels is to block their synthesis. Glucose metabolism feeds into FA metabolism at the point of citrate, an intermediate in the Krebs cycle (see Figure 1). Several steps are required to convert carbons from citrate to bioactive fatty acids. These steps involve ATP citrate lyase (ACLY, ACL, or ATPCL), acetyl-CoA carboxylase (ACC), fatty acid synthase (FASN or FAS), and acyl-CoA synthetase also known as fatty acid-CoA ligase (ACS, ACSL or FACL). In the model of decreasing FA availability, inhibiting these enzymes would limit cancer cell growth. Important for the clinical significance of these strategies, many inhibitors of these enzymes have minimal effects on non-cancer cells.

The subcellular localization of citrate determines its metabolic fate: mitochondrial citrate feeds into the Krebs cycle, and cytoplasmic citrate feeds into FA synthesis. Citrate is transported across the inner mitochondrial membrane for use in the cytoplasm in a regulated fashion by the transport protein CIC (**ci**trate **c**arrier). CIC levels are elevated in various cancer cell lines and tumors in a manner correlated with poor outcomes, and the inhibition of transport by benzene-tricarboxylate analog (BTA) shows anti-tumor effects in various tumor types and *in vivo* in xenograft mice (Catalina-Rodriguez et al., 2012).

ACLY—ACLY bridges glucose metabolism and FA metabolism by converting six-carbon citrate to oxaloacetate and two-carbon acetyl-CoA, the precursor for FA synthesis. Knockdown of ACLY reduces the ability of cells to metabolize glucose to lipid as shown by shRNA in murine lymphoid cells (Bauer et al., 2005) and siRNA in human adenocarcinoma cells (Hatzivassiliou et al., 2005). This alteration in metabolism impairs murine tumorigenesis and prevents xenograft tumor formation by human cancer cells when ACLY is knocked down by shRNA (Bauer et al., 2005; Hatzivassiliou et al., 2005) or siRNA (Migita et al., 2008) or chemically inhibited by SB-204990 (Hatzivassiliou et al., 2005). While ACLY is a promising therapeutic target, its product acetyl-CoA is an important metabolite for many molecules and a substrate for the acetylation of proteins and nucleic acids (Wellen et al., 2009). Thus, inhibiting its production may have consequences for other metabolic pathways as well.

ACC—ACC carboxylates acetyl-CoA to form malonyl-CoA, catalyzes the committed step, and is the most highly regulated enzyme in the fatty acid synthesis pathway (reviewed in

Wakil and Abu-Elheiga, 2008). ACC is positively and allosterically regulated by citrate and glutamate and negatively and allosterically regulated by long- and short-chain fatty acyl CoAs such as palmitoyl-CoA. ACC is inactivated by phosphorylation by AMP-activated protein kinase (AMPK) and potentially regulated by many other kinases. There are two ACCs in the human genome, ACC1 (ACCα or ACACA) and ACC2 (ACCβ or ACACB). ACC1 is highly enriched in lipogenic tissues, and ACC2 occurs in oxidative tissues. Because they are primarily found in different specialized tissues, ACC1 and ACC2 have different metabolic roles. Malonyl-CoA made by ACC1 is thought to serve as a substrate for FA synthesis, whereas the malonyl-CoA made by ACC2 serves to inhibit CPT1 (see next section), thus preventing FA degradation.

Knockdown of ACC1 by siRNA induces apoptosis in prostate cancer (Brusselmans et al., 2005) and breast tumor (Chajès et al., 2006) cells but not in control non-malignant cells. Chemical inhibition of ACC1 and ACC2 by soraphen-A showed similar results in prostate cancer cells (Beckers et al., 2007). However, a contradictory result was observed with ACC inhibition by TOFA (5-(tetradecyloxy)-2-furoic acid) in breast cancer cells (Pizer et al., 2000). This may be attributable to epidermal growth factor receptor (EGFR) activation, as TOFA was observed by another group to block the growth of EGFR-activated human glioblastoma cell lines while not affecting non-EGFR activated cell lines (Guo et al., 2009a). The situation is further complicated by the observation that silencing of ACC1 or ACC2 accelerated tumor growth in lung cancer cells by promoting NADPH-dependent redox balance (Jeon et al., 2012).

While some aspects of the role of ACC in cancer cells still need to be elucidated, ACC activity might be controlled by promoting ACC phosphorylation. AMPK is activated by drugs, such as metformin, already widely used to treat diabetes. There is experimental evidence *in vitro* and *in vivo* in mice and humans, mainly in solid tumor models, that metformin treatment has anti-tumor activity, and clinical trials to further explore efficacy are underway (Pollak, 2012).

MCD—Malonyl-CoA decarboxylase (MCD) decarboxylates malonyl-CoA to acetyl-CoA, essentially reversing the reaction catalyzed by ACC. Thus, it is surprising that MCD inhibition yields similar data as ACC. siRNA against MCD and MPA treatment, a small-molecule inhibitor of MCD, are cytotoxic to breast cancer lines but not fibroblasts (Zhou et al., 2009).

FASN—FASN catalyzes successive condensation reactions to form a fatty acid from malonyl-CoA and acetyl-CoA substrates, producing mainly 16-carbon palmitate. It is perhaps the most studied FA metabolic enzyme with respect to cancer. Increased fatty acid synthesis due to increased levels of FASN has been observed in a multitude of cancers and is strongly correlated with a poor prognosis in many instances (reviewed in Menendez and Lupu, 2007). RNAi against FASN decreases levels of TG and phospholipids and inhibits cell growth and apoptosis in cells derived from a lymph node metastasis of prostate carcinoma (LNCaP) cells with no effects on growth rate or viability of non-malignant cultured skin fibroblasts (DeSchrijver et al., 2003). In many reports, chemical inhibitors of FASN preferentially killed cancer cells (reviewed in Lupu and Menendez, 2006). FASN is a particularly appealing therapeutic target because most cancer cells depend upon FASN-mediated *de novo* FA synthesis, whereas most non-cancer cells prefer exogenous FA. However, cell death induced after FASN inhibition might be due to the toxic accumulation of malonyl-CoA rather than a lack of FA (Pizer et al., 2000). Moreover, some inhibitors of FASN show severe side effects in animal models, including dramatic weight loss (Loftus et al., 2000), and FASN is required for adult neuronal stem cell function (Knobloch et al., 2012).

ACS—For FAs to enter bioactive pools, they must be activated by ACS enzymes, which generate FA-CoA. Bioactive FAs also contribute to protein palmitoylation, a post-translational modification that is important in certain cancers (Resh, 2012). Mammals have five ACS isoforms (ACSL1, 3, 4, 5, and 6) and also have fatty acid transport proteins with acyl CoA synthetase activity. ACSL4 is upregulated in some colon adenocarcinomas (Cao et al., 2000), and ACSL5 levels are increased in glioblastomas (Yamashita et al., 2000). Overexpression of ACSL4 promotes tumor cell survival by preventing apoptosis, likely through depletion of unesterified arachidonic acid (AA), which yields a pro-apoptotic signal (Cao et al., 2000). Chemical inhibition of ACS by Triacsin C (inhibitor of ACSL1, 3, and 4 but not 5 or 6 (Van Horn et al., 2005; Kim et al., 2001) preferentially induces apoptotic cell death in lung, colon, and brain cancer cells (Mashima et al., 2005). Several thiazolidinediones (TZDs) directly bind and inhibit rat ACSL4 (but not ACSL1 or ACSL5) *in vitro* (Kim et al., 2001). TZDs activate peroxisome proliferator-activated receptors (PPARs), particularly PPARγ, and are already in wide use for the treatment of diabetes. TZD use is correlated with decrease incidence of certain cancers in diabetics in what is likely to be a PPARγ-independent manner (Weng et al., 2006). When considering treatment through inactivation of ACS, it is important to note that different drugs have different isoform specificities so they may have differential effects, as the various isoforms have different tissue specificities, responses to nutritional state (Mashek et al., 2006), and preferred substrates (notably, ACSL4 prefers AA).

SCD—SCD catalyzes the introduction of double bonds into short-chain FAs in the C9 position (mainly converting stearoyl-CoA to oleoyl-CoA) (Paton and Ntambi, 2009). This alters the physical properties of FAs and has profound effects on lipid function. There are two isoforms of SCD in human cells (SCD1 and SCD5). SCD expression and activity is upregulated in some cancers, and its importance for cancer biology is increasingly recognized (Igal, 2010). Inhibition of SCD function causes cell death in cancer cells, probably by inducing the accumulation of unsaturated fatty acids (Ariyamo et al., 2010). Pharmacological inhibition of SCD limits tumor growth in pre-clinical cancer models (Fritz et al., 2010) without affecting overall body weight (Roongta et al., 2011). Since cancer cells rely considerably on de novo FA synthesis, SCD inhibition will likely show some degree of selectivity.

FAs are also substrates for sphingolipid synthesis. While sphingolipid metabolism is not a focus of this review, it is noteworthy that specific sphingolipids, such as ceramides and sphingosine-1-phosphate, are bioactive signaling molecules that generally suppress or promote tumors, respectively (Ogretmen and Hannun, 2004). Moreover, accumulation of ceramides is implicated in the therapeutic effects of various chemotherapeutic treatments of cancer.

Blocking Expression of Fatty Acid Synthesis Genes

In addition to directly targeting enzymes of fatty acid synthesis, their activities could be reduced by reducing transcription levels. The master transcriptional regulators of FA synthesis are sterol regulatory element-binding protein 1 (SREBP-1) transcription factors (Horton et al., 2002). SREBP-1 has two isoforms: SREBP-1a is the predominant isoform in most cultured cell lines and SREBP-1c is predominant in liver and most tissues. At normal levels, SREBP-1c activates the FA biosynthetic pathway with responsive genes including ACLY, ACC, FAS, SCD-1, and GPAT. Therefore, inhibiting SREBP-1 in cancer cells could decrease fatty acid synthesis gene expression and possibly prevent cancer cell proliferation. Indeed, shRNA knockdown of SREBP-1 decreases abundance of ACC and FAS and promotes tumor cell death of glioblastoma cells that overexpress SREBP-1 because of constitutively active EGFR, and 25-hydroxycholesterol (25-HC), an inhibitor of activation

of SREBP-1 and -2, causes cell death in high EGFR (and therefore high SREBP-1) expressing cancer cell lines (Guo et al., 2009b). Additionally, higher levels of SREBP-1 are seen in prostate cancer tissue and both SREBP-1 and -2 play a role in the prostate cancer progression to androgen independence (Ettinger et al., 2004). Interestingly, recent work suggests that a mechanism for SREBP-1 repression preventing cancer cell proliferation is through loss of SCD-1 and FA desaturation, thereby causing lipotoxicity due to abnormally high levels of saturated FAs (Williams et al., 2013; Griffiths et al., 2013). Inhibition of SREBP by 25-HC, fatostatin, and FGH10019 all cause a decrease in expression of SREBP-1 and -2 target genes and significantly reduce cellular growth in a variety of cancer cell lines (Williams et al., 2013) and SREBP1 knockdown by shRNA reduces tumor growth *in vivo* in nude mice (Griffiths et al., 2013).

Further upstream, SREBP transcription factors and FA synthesis can be regulated by many signaling pathways, including growth factor signaling, which is reviewed in depth elsewhere (Shao and Espenshade, 2012; Kumar-Sinha et al., 2003; Peterson et al., 2011; Laplante and Sabatini, 2009; Lewis et al., 2011). Another transcription factor, liver X-activated receptor (LXR), activates fatty acid synthesis by inducing SREBP-1c (Liang et al., 2002). Therefore, cancer cell proliferation might be attenuated by preventing LXR activation. However, activation of LXR, particularly through T0901317, inhibits cancer cell proliferation in breast, colon, and prostate cancers (Viennois et al., 2012). These findings likely reflect functions of LXR other than regulating FA synthesis.

Increasing Fatty Acid Degradation

FA levels might be decreased in cancer cells by increasing the rate at which they are degraded. Activated FAs are broken by mitochondrial β-oxidation. FA-CoAs are transported from the cytosol across the outer mitochondrial membrane after they are converted to FA carnitines by carnitine palmitoyl transferase 1 (CPT1). Within the mitochondria, FAs are then repeatedly cleaved to produce acetyl-CoAs that feed into the Krebs cycle and produce reducing equivalents for oxidative phosphorylation. Increasing FA oxidation to limit FA abundance could in theory be beneficial, but data from experiments testing this idea are mixed.

CPT1—CPT1 is the first and rate-limiting step of fatty acid transport into mitochondria for oxidation to carbon dioxide. It is inhibited by malonyl-CoA. β-Oxidation of FAs is increased when ACC2 is inhibited because of the depletion of malonyl-CoA, the direct product of ACC. Therefore, the attenuation of cancer cell proliferation by inhibiting ACC (discussed previously) may also be due in part to an increase in degradation of FAs.

It is yet unclear whether increased FA oxidation in cancer cells will block proliferation. Cancer types likely differ in their clinical response to increasing FA oxidation, depending upon their energy requirements and ACC isoform expression patterns. In some types, increased FA oxidation may diminish FA availability and be beneficial. On the other hand, etomoxir, an inhibitor of CPT1, and ranolazine, an indirect inhibitor of FA oxidation, may kill cancer cells (Samudio et al., 2010; Pike et al., 2011). A further caveat of increasing the FA oxidation rate is that it could increase cellular ATP levels, thus providing energy for further cellular proliferation. Indeed, CPT1C, the brain isoform of CPT1, is important for the survival of cancer cells under energy stress (Zaugg et al, 2011).

It has long been known that PPARα is a major transcriptional regulator of FA oxidation with activation inducing oxidation. In keeping with the uncertainty regarding the role of FA oxidation in cancer cell proliferation, extended PPARα activation causes hepatocellular carcinoma in mice and rats by an unclear mechanism that involves perturbation of the cell cycle and production of reactive oxygen species (reviewed by Michalik et al., 2004).

However, humans taking PPARα agonists do not develop similar cancers, and in fact, PPARα activation inhibits tumor growth in several models (reviewed in Yokoyama and Mizunuma, 2010).

Diverting Fatty Acids to Storage

Once made, FAs can be used for membrane lipid synthesis, degraded, or stored. Conceivably, increased storage of FAs in neutral lipids, such as TGs or sterol esters, could lead to a reduction in FAs available for use as membrane building blocks or signaling lipids and inhibit cellular proliferation. Most cells store FAs in TGs in the cytosolic lipid droplet (LD), an organelle whose major function is lipid storage (see Farese and Walther, 2009). The role of LDs in cancer cells is unclear. While increased numbers of LDs have been reported in many cancer cells (reviewed in Bozza and Viola, 2010), and this accumulation has been proposed to be pathogenic, the accumulation of LDs per se, might not be the culprit. The readily available pool of FAs that they represent might be pathogenic. LD accumulation might also reflect a cellular response to stress (Hapala et al., 2011). Future studies should also carefully delineate whether LD accumulation occurs within cancer cells or in surrounding cells.

The major TG synthesis pathway is known as the Kennedy or glycerol-phosphate pathway. It condenses FAs with glycerol 3-phosphate using the enzymes glycerol-3-phosphate acyltransferase (GPAT), acylglycerolphosphate acyltransferase (AGPAT), phosphatidic acid phosphohydrolase (Lipin or PAP), and diacylglycerol acyltransferase (DGAT). The products of all but the most distal enzyme (DGAT) feed into PL synthesis. Therefore, GPAT, AGPAT and Lipin might be inhibited to limit PL production, while efforts to increase FA storage would be focused on activating DGAT. Additionally, the potential benefits of increasing FA storage may only be realized while concomitantly inhibiting the release of FA from storage.

AGPAT—AGPAT esterifies lysophosphatidic acid (LPA) and a FA-CoA to form phosphatidic acid (PA). There may be as many as 11 human AGPATs. Elevated AGPAT2 expression is associated with poor prognosis of ovarian cancers, and AGPAT2 inhibitors have antitumor activity in xenograft mice (reviewed in Takeuchi and Reue, 2009). Additionally, AGPAT9 and AGPAT11 are upregulated in a variety of cancers (reviewed in Agarwal, 2012). As with any enzyme with multiple isoforms, differences in expression patterns of the isoforms may have a profound influence on the effectiveness of inhibition/activation of a particular isoform in a particular cancer.

PAP—Lipin removes a phosphate group from PA to form diacylglycerol (DG). It is one of the least-studied enzymes in the lipid storage pathway with respect to cancer, and little is known about how blocking or overexpressing this step of lipid synthesis affects cancer progression. However, lipin is involved in the regulation of the activity of sterol regulatory element binding proteins (SREBP), a family of transcription factors that regulate the expression of many enzymes involved in fatty acid and cholesterol biosynthesis (Ishimoto et al., 2009). Lipin is phosphorylated and inhibited by the mammalian target of rapamycin complex 1, resulting in activation of SREBP transcriptional activity (Peterson, et al., 2011). Modulating lipin activity may therefore have significant effects on cellular lipid homeostasis.

DGAT—DGAT enzymes esterify DG and a FA-CoA to form TG. Mammals have two DGATs (DGAT1 and DGAT2). DGAT catalyzes the only dedicated step in TG formation and thus provides a key target for decreasing available lipids by increasing lipid storage. Transformed human fibroblasts overexpressing DGAT1 had increased TG and decreased

phospholipids, as well as reduced proliferation and invasiveness (Bagnato and Igal, 2003). Unpublished data from the Farese laboratory suggests that DGAT1-deficient mice have increased levels of LPA and PGE2 in mammary fat and develop some breast cancers more rapidly (Sylvaine Cases, unpublished). DGAT1 inhibition might also favor the accumulation of its substrate diacylglycerol in cells, which might have signaling effects. These findings would suggest caution, from a cancer standpoint, for the use of DGAT1 inhibitors, which are being explored clinically for use in metabolic diseases.

PLs are the other major products of glycerolipid synthesis and are important for membrane expansion in rapidly proliferating cells. The major mammalian membrane phospholipid is PC. Many cancers have increased PC levels and increased activity of any of several enzymes in the PC synthesis pathway, while inhibition or knockdown of many of the enzymes decrease cancer phenotypes (Glunde et al., 2011). An inhibitor of choline kinase alpha (CKα), the first step of choline activation for PC synthesis, is currently in Phase I trials for use against advanced solid tumors (http://clinicaltrials.gov/show/NCT01215864).

Blocking Fatty Acid Release From Storage

Once stored, FAs can be released for use by specific lipases. By preventing lipolysis, the active FA pool available for cancer cell proliferation might be decreased. FAs derived from lipolysis can also serve as precursors for important signaling lipids (see Wymann and Schneiter, 2008). Most knowledge on lipolysis is derived from work on adipocytes where each TG molecule in the LD can be fully hydrolyzed to release three FAs by the sequential action of adipose triglyceride lipase (ATGL), hormone sensitive lipase (HSL) and monoacylglycerol lipase (MAGL). Although each of these lipases also has important functions in other tissues, it is yet unclear whether other lipases might operate in other cell types. Currently, most data addressing lipases and cancer are for MAGL.

MAGL—MAGL hydrolyzes the final FA from MG leaving the glycerol backbone. MAGL expression and activity are increased in several aggressive cancer cell lines and primary tumors (Nomura et al., 2010). Knockdown and chemical inhibition of MAGL by JZL184 lowered free FA levels and reduced pathogenicity of melanoma and ovarian cancer cells in vitro and in vivo, while overexpression showed the opposite phenotype. Interestingly, a high-fat diet in mice reversed the reduced tumor growth of MAGL-inhibited tumors in mice. This observation raises the question of whether targeting lipid metabolism for cancer therapy may only be effective in combination with specific dietary regimes. Additionally, MAGL has a role in the regulation of signaling lipids: more invasive tumors have increased LPA and PGE_2 levels, and those are decreased in the presence of MAGL inhibitors.

ATGL and HSL—Although their roles in cancer cell proliferation are unclear, ATGL and HSL play an important role in cancer cachexia, a wasting syndrome that is an adverse prognostic factor in cancer. Cancer patients with cachexia show increased HSL and ATGL activity when compared to non-cancer patients, and genetic ablation of ATGL (and HSL to a lesser extent) protects mice from cancer-associated loss of adipose tissue and skeletal muscle (Das et al., 2011). Therefore, pharmacological inhibition of ATGL and/or HSL may help to prevent cancer-associated cachexia.

Conclusion and Perspective

Cancer cells rely on FAs as cellular building blocks for membrane formation, energy storage, and the production of signaling molecules. Our review highlights this requirement and provides a framework for the investigation of limiting the supply of FAs. If the model that FAs are required for cancer cell proliferation is correct, cancer cells might be targeted at multiple points within the pathway of FA metabolism to subvert rapid proliferation, and

many chemical inhibitors for specific steps already exist (Table 1). Much like glucose metabolism, targeting FA metabolism might be more selective for highly proliferative cells. Alternatively, delivery of FA metabolism inhibitors might be done in a cell-specific and targeted manner.

Cancers are diverse in type and underlying genetic alterations. Lipid metabolism is complex, with many different feedback mechanisms and points of regulation. Additionally, most of the lipid metabolic enzymes have multiple isoforms, and these may be coupled to different lipid metabolic processes and can have different cellular localization or tissue distribution. Therefore, successful therapies may be dependent upon understanding the specific metabolic abnormalities for a particular type of cancer.

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Abbreviations

AA	arachidonic acid
ACC	acetyl-CoA carboxylase. Carboxylates Acetyl-CoA to form malonyl-CoA
ACS/ACSL	acyl-CoA synthetase. Also known as Fatty Acid Co-A Ligase. Activates a fatty acid to a fatty acyl-CoA
ACL/ATPCL/ ACLY	ATP citrate lyase. Converts citrate to acetyl-CoA
AGPAT	acylglycerophosphate acyltransferase. Condenses LPA and a FA-CoA to form PA
ATGL	adipose triglyceride lipase. Hydrolyzes TG to DG and a FA
CIC	citrate carrier protein
CPT1	carnitine palmitoyl transferase 1. Transports FA-CoAs across the mitochondrial membrane for degradation
DG/DAG	diacylglycerol. Contains a glycerol backbone and two fatty acids
DGAT	diacylglycerol acyltransferase. Adds a FA to DG to form TG
FA	fatty acid
FACL	fatty acid Co-A ligase. See ACS
FAS/FASN	fatty acid synthase. Condenses malonyl-CoA and acetyl-CoA to form a fatty acid
GPAT	glycerol-3-phosphate acyltransferase. Condenses glycerol-3-phosphate and a FA-CoA to make LPA
HSL	hormone sensitive lipase. Hydrolyzes DG to MG and a FA
LD	lipid droplet. An organelle whose major functions include lipid storage
LPA	lysophosphatidic acid
LXR	liver X-activated receptor
MG/MAG	monoacylglycerol. Contains a glycerol backbone and one fatty acid

MAGL	monoacylglycerol lipase. Hydrolyzes MG to glycerol and a FA
MCD	malonyl-CoA decarboxylase. Decarboxylates malonyl-CoA to acetyl-CoA
PA	phosphatidic acid
PAP	phosphatidic acid phosphohydrolase. Removes a phosphate from PA to form DG. Also known as lipin
PGE2	prostaglandin E2
PL	phospholipid
PPAR	peroxisome proliferator-activated receptor. Three family members include α, β /δ, and γ
PPP	pentose phosphate pathway. Also known as phosphogluconate pathway or the hexose monophosphate shunt. Generates NADPH for fatty acid synthesis
SCD	stearoyl-CoA desaturase. Introduces double bonds into short-chain FAs
SE	sterol ester. A sterol backbone and a FA
SREBP-1	sterol response element binding protein-1. The major FA regulatory transcription factor. Has two isoforms, SREBP-1a and SREBP1-c
TG/TAG	triacylglycerol. The major lipid stored in most lipid droplets. A glycerol backbone and three fatty acids

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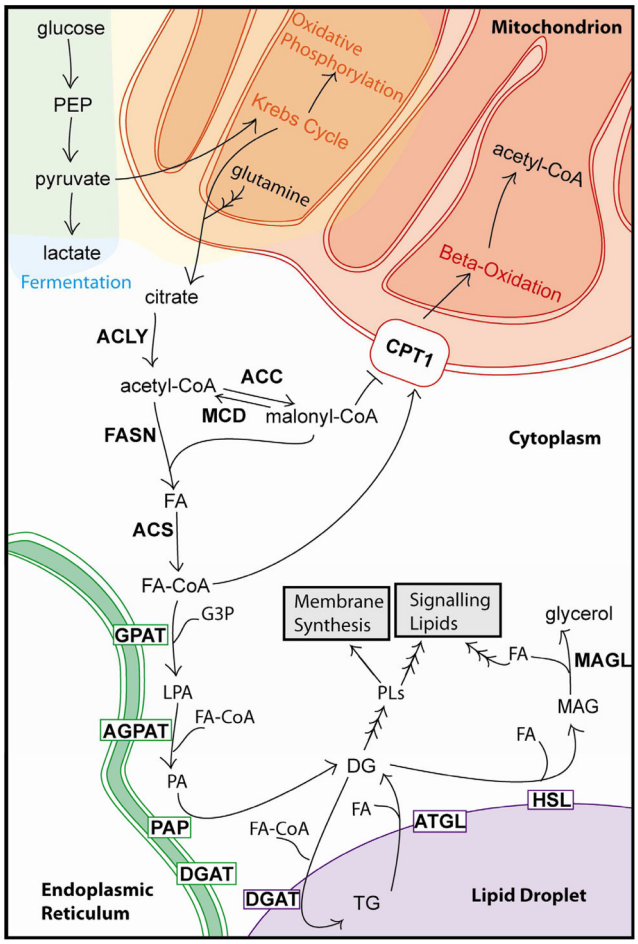

Figure 1. Overview of cellular fatty acid metabolism

See text for description of depicted pathways. Enzymes are in bold. Enzymes with boxes around them are membrane localized.

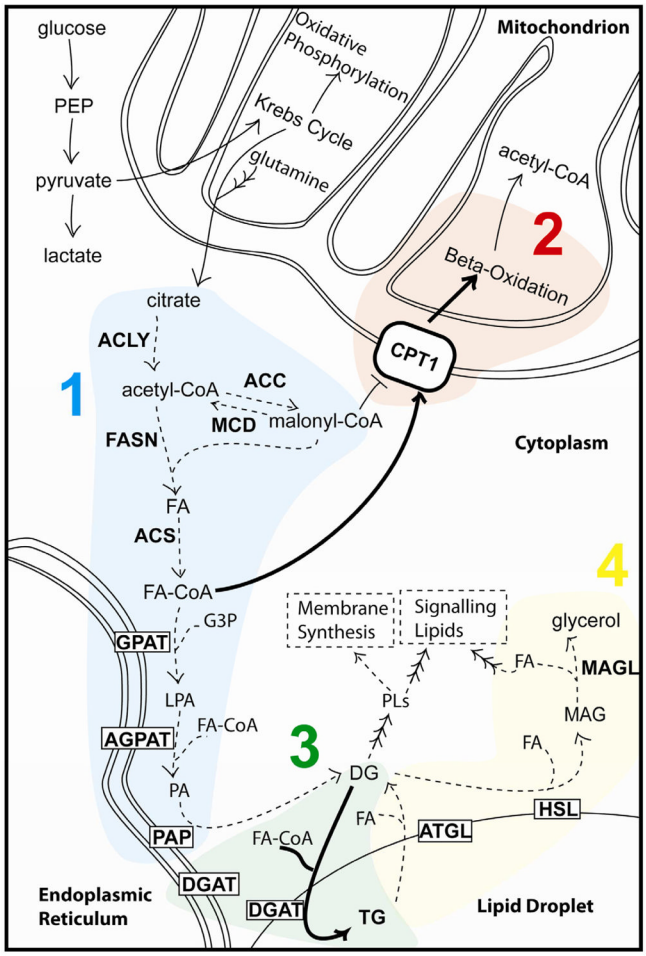

Figure 2. Model showing how limiting FAs in the cell might limit cancer cell proliferation

This may be done by 1) blocking the synthesis of fatty, 2) increasing the rate of FA degradation, 3) increasing FA storage in neutral TG, and/or 4) decreasing FA release from storage.

Table 1

Examples of chemical inhibitors of lipid enzymes that could reduce fatty acid availability. Shown are selected inhibitors for enzymes mentioned in text.

Enzyme	Inhibitor	Comments	Selected References
ACC	Soraphen-A		(Beckers et al., 2007)
	TOFA (5-(tetradecyloxy)- 2-furoic acid)		(Pizer et al., 2000), (Guo et al., 2009a)
	A-769662		(Göransson et al., 2007)
	Metformin	Indirect, activates AMPK	(Pollak, 2012)
	AICAR	Indirect, activates AMPK	(Jose et al., 2011)(Swinnen et al., 2005)
ACLY	SB-204990		(Hatzivassiliou et al., 2005), (Ros et al., 2012)
	LY294002	Indirect, PI3K inhibitor	(Migita et al., 2008)
ACS	Triacscin C		(Mashima et al., 2005)
	Thiazolidinediones (TZDs)	ACSL4 specific, also activates PPARγ, FDA approved	(Kim et al, 2001)
AGPAT	CT-32501	AGPAT2 specific	(Takeuchi and Reue, 2009)
CKα	TCD-717	Currently in phase I trials	http://clinicaltrials.gov/show/NCT01215864
	MN58B		(Glunde et al., 2011)
CIC	Benzene-tricarboxylate analog (BTA)		(Catalina-Rodriguez et al., 2012)
CPT1	Etomoxir		(Samudio et al., 2010) (Pike et al., 2011)
	Ranolazine	FDA approved	(Samudio et al., 2010)
FASN	Cerulenin and its derivative C75		(Lupu and Menendez, 2006) (Ros et al., 2012)
	Orlistat	FDA approved	(Lupu and Menendez, 2006)
	Flavonoids	Naturally occurring	(Lupu and Menendez, 2006)
	Epigallocatechin-3-gallate (EGCG)	Found in green tea	(Lupu and Menendez, 2006)
MAGL	JZL184		(Nomura et al., 2010)
SCD	BZ36		(Fritz et al., 2010)
	A939572		(Roongta et al., 2011)
SREBP	Fatostatin	Inhibits processing of SREBP-1 and -2	(Williams et al, 2013)
	FGH10019	Inhibits processing of SREBP-1 and -2	(Williams et al, 2013) (Kamisuki et al, 2011)