

Review Article

Lipid metabolism in prostate cancer

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Abstract: The malignant transformation of cells requires adaptations across multiple metabolic processes to satisfy the energy required for their increased rate of proliferation. Dysregulation of lipid metabolism has been a hallmark of the malignant phenotype; increased lipid accumulation secondary to changes in the levels of a variety of lipid metabolic enzymes has been documented in a variety of tumors, including prostate. Alterations in prostate lipid metabolism include upregulation of several lipogenic enzymes as well as of enzymes that function to oxidize fatty acids as an energy source. Cholesterol metabolism and phospholipid metabolism are also affected. With respect to lipogenesis, most studies have concentrated on increased expression and activity of the *de novo* fatty acid synthesis enzyme, fatty acid synthase (FASN), with suggestions that FASN might function as an oncogene. A central role for fatty acid oxidation in supplying energy to the prostate cancer cell is supported by the observation that the peroxisomal enzyme, α -methylacyl-CoA racemase (AMACR), which facilitates the transformation of branched chain fatty acids to a form suitable for β -oxidation, is highly overexpressed in prostate cancer compared with normal prostate. Exploitation of the alterations in lipid metabolic pathways in prostate cancer could result in the development of new therapeutic modalities as well as provide candidates for new prognostic and predictive biomarkers. AMACR has already proven to be a valuable biomarker in distinguishing normal from malignant prostate tissue, and is used routinely in clinical practice.

Keywords: Prostate cancer, lipogenesis, fatty acid oxidation

Cancer cell survival requires metabolic alterations

The uncontrolled growth characteristic of malignant transformation requires adaptive alterations in intermediary metabolism to satisfy the energy requirements and biochemical needs of a rapidly dividing cell. Many cancers depend on glycolysis to achieve this goal, a phenomenon first described in the early part of the 20th century by Otto Warburg [1]. He suggested that the increase in glucose utilization *via* glycolysis was due to an inherent defect in the oxidative phosphorylation mechanism in the malignant cell, and further postulated that this defect in oxidative phosphorylation was a cause of cancer. Although this hypothesis has been proven to be incorrect, in that cancer cells do not have inherent defects in oxidative phosphorylation [2], the observation that cancer cells exhibit increased glycolysis and glucose utilization has proven to be the case for the majority of malignancies, and the Warburg Hypothesis as currently understood refers to the increased glu-

cose utilization characteristic of the malignant state [3-5]. Furthermore, this increased utilization of the glycolytic pathway can occur even in the presence of adequate oxygen, thus the glycolysis of malignancy has been termed aerobic glycolysis, even though there is no requirement for oxygen. The increase in glucose utilization forms the basis for a diagnostic imaging technique known as positron-emission tomography (PET), in which uptake of a glucose analog is monitored as an indicator of malignancy [6]. While enhanced glucose metabolism provides a nutrient source and the energy required for subsequent synthesis of the macromolecular components, such as lipids that are necessary for cellular proliferation, as shown in **Figure 1**, it has also been noted that there are alterations in the expression of the enzymes that function to facilitate synthesis of these macromolecules as well as in the expression of protein entities, such as growth factors, transcription factors and receptors that are involved in regulating these pathways. There appears to be a global alteration in the metabolome of cancer cells

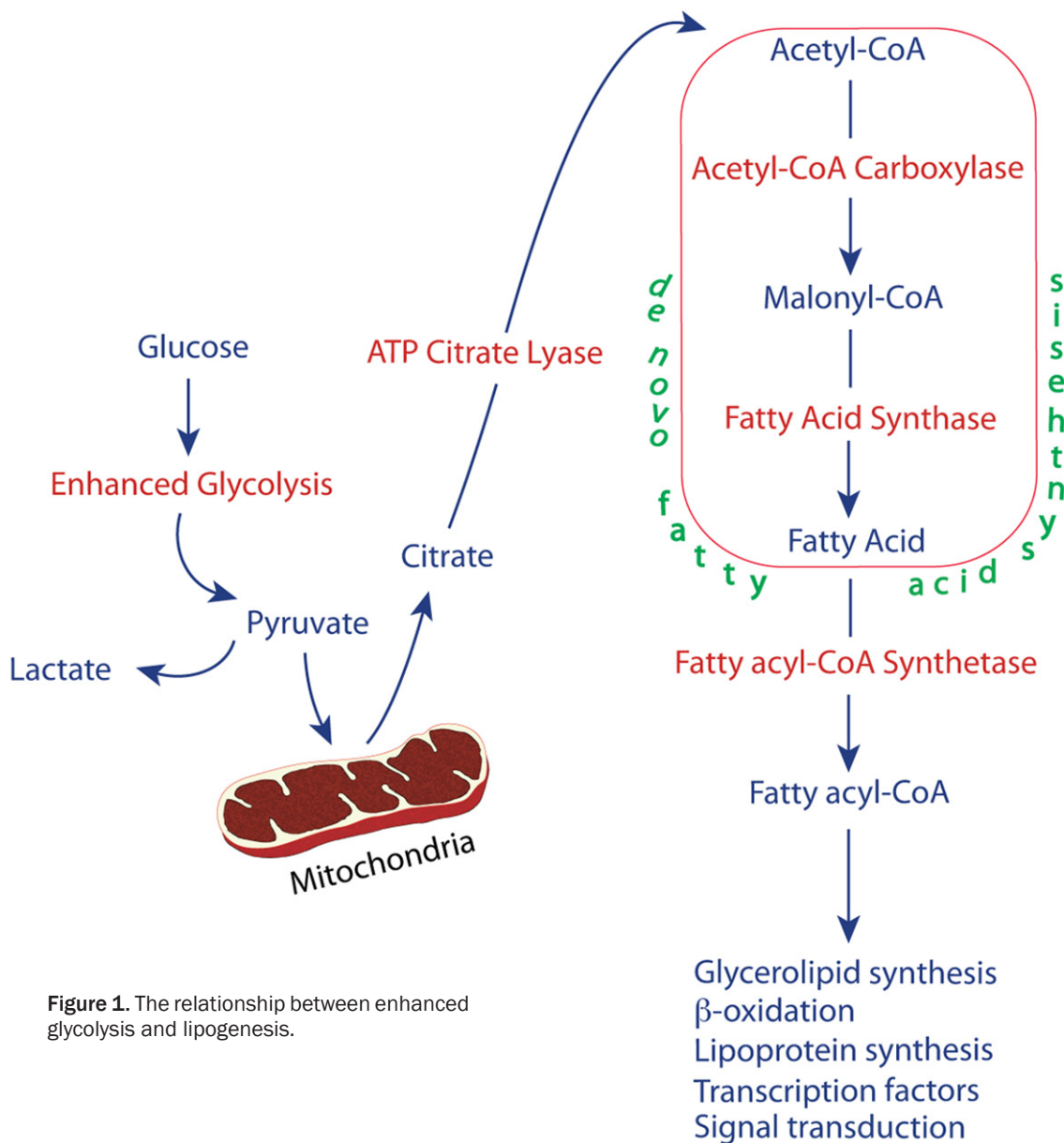


Figure 1. The relationship between enhanced glycolysis and lipogenesis.

that provides a growth and survival advantage that may be specific to various stages of tumor progression, and may even serve as a the basis for prognostic biomarkers as well as for chemotherapeutic targets [7].

Prostate cancer exhibits a unique metabolic adaptation

The normal prostate has a unique intermediary metabolic profile in that it functions as a source of secreted citrate and zinc. The production of large amounts of citrate required for secretion into prostatic fluid is bioenergetically costly, and prostate epithelial cells naturally turn to aerobic glycolysis to compensate for the loss.

Thus under normal circumstances prostate cells derive energy *via* aerobic glycolysis, with less dependence on aerobic oxidation. Malignant prostate cells, on the other hand, increase levels of oxygen consumption in order to support uncontrolled proliferation. As a result, the large amount of citrate that would normally be secreted, can now function as an intermediate in the citric acid cycle as well as a substrate for *de novo* fatty acid synthesis [8, 9].

Lipid metabolism is important in prostate cancer

The role of lipid metabolism in the development and progression of prostate cancer has been

Table 1. Lipogenic enzyme mRNA expression in normal and cancerous human prostate

Enzyme	Study	Fold Change	p-value	n
ACLY	Singh [26]	2.98	1.33e-05	50, 52
	Welsh [27]	2.12	9.12e-06	9, 25
	Wallace [29]	2.31	0.001	20, 69
ACACA	Vanaja [28]	2.38	1.86e-06	8, 27
	Luo [31]	1.64	0.002	15, 15
	Lapointe [30]	1.72	2.31e-13	41, 61
	Welsh [27]	1.46	2.80e-06	9, 25
FASN	Singh [26]	5.64	1.96e-06	50, 52
	Welsh [27]	3.21	4.90e-08	9, 25
	Wallace [29]	3.68	1.55e-04	20, 69
	Vanaja [28]	3.20	7.65e-05	8, 27
ACSL1	Singh [26]	2.21	3.45e-05	50, 52
	Welsh [27]	1.48	0.001	9, 25
	Wallace [29]	1.60	0.009	20, 69
ACSL3	Singh [26]	1.78	1.09e-04	50, 52
	Lapointe [30]	1.50	1.68e-06	41, 62
	Welsh [27]	1.60	5.85e-04	9, 25
ACSL4	Singh [26]	-1.48	0.009	50, 52
	Welsh [27]	-1.93	3.14e-04	9, 25
	Grasso [25]	-1.48	1.92e-05	28, 59
ACSL5	Grasso [25]	2.12	8.24e-09	28, 59
	Lapointe [30]	1.37	1.02e-05	41, 60
SREBP1	Wallace [29]	1.53	2.41e-04	20, 69
	Welsh [27]	1.72	4.19e-04	9, 25
	Singh [26]	2.05	0.031	50, 52

Fold change = cancer/normal. n = number of samples (normal, cancer). Data taken from Oncomine [24].

investigated on several levels. While the relationship between obesity and the risk of developing prostate cancer is not yet clear, that between obesity and death from prostate cancer has been more firmly established [10]. And the crucial importance of lipids, including fatty acids, phospholipids and cholesterol in the expression of the malignant phenotype is clear [11, 12]. Data suggest that a variety of mechanisms may function to fulfill the need for lipids, including uptake of circulating lipids [13], transfer of fatty acids from stromal adipocytes to prostate cancer cells [14], increased *de novo* synthesis of fatty acids [15] and phospholipids [16, 17], and increased accumulation of cholesterol as cholesteryl ester stored in cytosolic lipid droplets [18]. The role of increased fatty acid oxidation as a source of energy in prostate cancer has been suggested [19], and the pro-found overexpression of the peroxisomal

enzyme, α -methylacyl-CoA racemase (AM-ACR), that is required for oxidation of branch-chained fatty acids, supports this hypothesis [20]. One can envision a balance between lipid synthesis and oxidation that functions to provide both the lipids and the energy required to support the growth and survival of prostate cancer.

Lipid synthesis is increased in prostate cancer

In most human tissues, the *de novo* pathway of fatty acid synthesis is of minor importance, the exceptions being liver and mammary gland, and, to a lesser extent, adipose tissue [21]. The cellular requirement for fatty acids is generally met by utilization of dietary fatty acids. Under normal conditions, *de novo* fatty acid synthesis is suppressed by circulating dietary fatty acids. Cancer cells, however, are insensitive to this product inhibition, and actively synthesize fatty acids despite what would normally be considered an inhibitory level of circulating fatty acids. So, as with many other pathological aberrations, the alteration in *de novo* fatty acid synthesis in malignancy is likely one of dysregulation. Prostate cancer cells exhibit increased expression of many lipogenic enzymes, often as a result of stimulation by oncogenic signaling pathways such as PI3K/AKT and HER2 [12]. Conversely, increased expression of fatty acid synthetic enzymes has been linked to activation and nuclear localization of Akt/PKB in clinical tumor samples [22]. Androgens have been demonstrated to increase the activity of lipogenic enzymes [23]. A survey of the gene expression database, Oncomine [24], reveals that mRNAs encoding lipid metabolic enzymes, including those involved in *de novo* fatty acid synthesis (ATP citrate lyase (ACLY), acetyl-CoA carboxylase α (ACACA), fatty acid synthase (FASN), and long chain fatty acyl-CoA synthetases 1, 3 and 5 (ACSL1, ACSL3, ACSL5)) are increased in prostate cancer, as is that of the transcription factor, sterol regulatory binding protein 1 (SREBP1), that regulates expression of fatty acid and cholesterol synthesizing enzymes. In an analysis of published data from multiple separate studies detailed in the Oncomine database, ACLY mRNA expression is significantly increased in 11/22 and decreased in 2/22

Table 2. β -oxidation enzyme mRNA expression in normal and cancerous human prostate

Enzyme	Study	Fold Change	p-value	n
CPT1B	Luo [31]	11.74	4.46e-04	15, 15
	Wallace [29]	1.94	1.21e-04	20, 69
	Welsh [27]	6.82	2.17e-05	9, 25
AMACR	Grasso [25]	13.05	4.57e-24	28, 59
	Welsh [27]	10.07	2.60e-13	9, 25
	Lapointe [30]	7.22	4.11e-23	40, 62
	Vanaja [28]	8.69	7.86e-11	15, 15

Fold change = cancer/normal. n = number of samples (normal, cancer). Data taken from Oncomine [24].

studies; ACACA mRNA is increased in 14/21 and decreased in 1/21; FASN mRNA is increased in 12/22 and decreased in 3/22; ACSL1 mRNA is increased in 5/22 and decreased in none; ACSL3 mRNA is increased in 8/20 and decreased in 1/20; and ACSL5 is increased in 6/12 and decreased in none. Expression of SREBP1 mRNA is increased in 8/22 studies and decreased in 2/22. **Table 1** summarizes data from several representative studies [25-31] that indicate the fold change and statistical significance of this mRNA overexpression in human tumor samples. The importance of cholesterol metabolism has also recently been reaffirmed. Enhanced cholesteryl ester accumulation in cellular lipid droplets was demonstrated to be associated with prostate cancer aggression [18]. In addition, it has been suggested that high circulating levels of cholesterol are positively associated with the development of prostate cancer [32].

ACLY

As noted in **Figure 1**, acetyl CoA required for fatty acid synthesis is derived *via* metabolism of citrate by the enzyme ACLY. Not only is expression of the mRNA that encodes this enzyme increased in prostate cancer, as illustrated in **Table 1**, but downregulation of its expression in prostate cancer cells either by pharmacologic reagents or siRNA treatment results in inhibition of proliferation [33, 34]. Its expression has been reported to be induced by androgen treatment [35].

ACACA

The rate-limiting step in the synthesis of fatty acids is the ATP-dependent conversion of acetyl CoA to malonyl CoA by the enzyme, ACAC.

Two isoforms have been identified, ACAC1 (also called ACACA) and ACAC2 (also called ACACB). Physiological control of ACAC activity is mediated by hormones and nutritional status, with SREBP1c playing a major role in regulating ACACA expression [36]. Inhibition of ACACA activity either pharmacologically or by RNA interference resulted in cessation of proliferation and cell death [37, 38]. Like ACLY, ACACA expression is stimulated by androgens [35].

FASN

The most extensively studied of the lipogenic enzymes in the context of carcinogenesis is FASN [39]. Overexpression of this enzyme has been reported for a variety of cancers, including prostate, liver, ovarian, colon, endometrial and breast, and has been associated with malignant transformation and a worse prognosis. In non-malignant tissues, such as liver, FASN activity is regulated by insulin and nutritional status *via* induction of a family of transcription factors, sterol regulatory element binding proteins (SREBP) that increase the expression of genes involved in lipid metabolism. The FASN of malignancy is non-responsive to nutritional status, and has been shown to be both regulated by [40], and able to regulate [22, 41], signal transduction pathways that are associated with the malignant phenotype. It has even been suggested that FASN, itself, functions as an oncogene [42]. Results from a number of studies suggest that FASN might serve as a biomarker of prostate cancer progression, with increased expression associated with a more aggressive phenotype [43, 44]. Transgenic expression of FASN in cultured prostate cancer cells increased the rate of proliferation and inhibited apoptosis, while FASN expression in human prostate tumor samples was inversely associated with the apoptotic rate [45]. High FASN expression in tumor samples was linked to activation and nuclear localization of Akt [22], and increased FASN was also associated with cytoplasmic stabilization of β -catenin [46]. Downregulation of FASN expression by siRNA, on the other hand, attenuated growth and induced apoptosis [47]. In a separate study [48], FASN inhibition not only suppressed cell proliferation but prevented pseudopodia formation and suppressed cell adhesion, migration, and invasion. FASN inhibi-

tion also suppressed genes involved in production of intracellular second messenger arachidonic acid and androgen hormones, both of which promote tumor progression. Androgens have been demonstrated to increase lipid accumulation [49] as well as FASN expression and activity in cultured prostate cancer cells [23]. Androgens have also been shown to increase FASN activity *via* increasing expression of ubiquitin-specific protease-2a, which, in turn, stabilizes FASN [50]. The 5-alpha reductase inhibitor, dutasteride, reduces FASN mRNA, protein and enzyme activity [51]. As with ACLY and ACACA, pharmacologic inhibition of FASN activity inhibits proliferation and induces cell death in prostate cancer cells, leading to the suggestion that FASN inhibition might be exploited in the treatment of prostate cancer [52]; however, to date, there has not been a viable inhibitor candidate for use in clinical trials due to unacceptable side effects.

Stearoyl-CoA desaturase-1 (SCD1)

The product of FASN activity is predominantly the saturated fatty acid, palmitic acid. Some evidence suggests that the proportion of mono-unsaturated fatty acids increases in prostate cancer [53], leading to the hypothesis that SCD1 activity may be increased in addition to FASN. Results are equivocal. In 2005, Moore et al [54] reported that SCD mRNA levels were downregulated in prostate cancer relative to normal prostate epithelium. These results were validated by qPCR and immunohistochemical analysis. The median SCD expression levels were 150, 45 and 10 for normal, PIN and carcinoma samples, respectively. However, Fritz et al. reported an increase in both SCD1 mRNA and protein expression in prostate cancer relative to normal prostate, and demonstrated that inhibition of SCD1 activity induces growth arrest of prostate cancer cells *in vitro* as well as *in vivo* [53]. A survey of the Oncomine database [24] likewise yields equivocal results: 7/20 analyses show increased mRNA expression in prostate cancer, while 5/20 show decreased expression.

ACSLs

Utilization of fatty acids for either synthesis of neutral and phospholipids or as substrates for β -oxidation requires an activation step cata-

lyzed by a fatty acyl-CoA synthetase (ACS) iso-enzyme that converts a free fatty acid to its respective CoA ester. The isoforms are characterized according to the chain length of their preferred substrate. The subset of isoenzymes that act on fatty acids with chain lengths between 16 and 22 carbons are referred to as long chain fatty acyl CoA synthetases (ACSLs). To date, 5 mammalian ACSLs that differ in sub-cellular location and substrate specificity have been identified [55]. The precise role of each isoform has not been delineated, but current evidence suggests that ACSL1 functions in hepatic glycerolipid synthesis [56, 57], while ACSL3 and ACSL5 seem to increase beta oxidation of fatty acids in certain cells [58]. The localization of ACSL4 to peroxisomes suggests that this enzyme may function in fatty acid oxidation [59]. Inhibitor studies indicate that ACSL4 may also be involved in hepatic triacylglycerol synthesis [60]. In prostate, ACSL3 has received the most attention due to its regulation by androgens [61]. While the level of ACSL3 mRNA expression increases in prostate cancer when compared with normal prostate epithelium (**Table 1**), it appears to be downregulated as a function tumor grade, with high grade and metastatic prostate cancer expressing comparatively lower levels of ACSL3 [61], suggesting a discordance between the growth and differentiation activities of the AR pathway. In prostate cancer cells lines, ACSL3 expression is highest in androgen sensitive cells [62], and treatment of androgen sensitive LNCaP cells with androgens increases expression of ACSL3 mRNA, while decreasing expression of ACSL1 and having no effect on ACSL4, 5, or 6 [63]. Upregulation of ACSL3 by vitamin D3 in LNCaP cells results in growth inhibition [64].

Expression of ACSL4 in prostate cancer cell lines appears to be inversely associated with that of ACSL3 [62], and evidence suggests that ACSL4 expression is associated with androgen-independent growth [65]. Interestingly, ACSL4 is the only isoform that displays decreased expression in cancer versus normal prostate tissue: ACSL4 mRNA expression is decreased in 10/15 analyses and increased in 1/15 (**Table 1**), yet appears to be a biomarker of androgen resistance and of a more aggressive phenotype of prostate cancer [65]. The same is true for ACSL4 expression in breast cancer [65-68].

Fatty acid oxidation is increased in prostate cancer

Although the emphasis with respect to dysregulation of lipid metabolism in cancer has been on lipogenesis and increased expression of lipogenic enzymes such as FASN, it is clear that fatty acid oxidation also plays a role in supporting the malignant phenotype [69]. A survey of mRNA expression data at Oncomine [24] indicates that a mitochondrial protein that is the rate-limiting step for mitochondrial β -oxidation, CPT1B, is elevated in prostate cancer samples in 12/21 analyses, and decreased in 2/21, while the peroxisomal enzyme that is required for β -oxidation of branched chain fatty acids, AMACR, is elevated in 16/20 analyses, and decreased in none. Representative individual study results are shown in **Table 2**. The relatively low level of aerobic glycolysis combined with the absence of the glucose transporter, GLUT1 [70], and the overexpression of AMACR [71] as well as of the β -oxidative pathway enzyme, DBP [72], in prostate cancer, support the hypothesis that fatty acid oxidation is a dominant bioenergetic pathway in prostate cancer, as proposed by Liu *et al* [19]. In addition to its utility as a biomarker, AMACR has also been demonstrated to have functional significance. Downregulation of AMACR expression *via* siRNA treatment in prostate cancer cells results in inhibition of proliferation [73], suggesting that AMACR might also serve as a target for therapy of prostate cancer [74].

Cholesterol metabolism in prostate cancer

There is ample data supporting a functional relationship between cholesterol metabolism and prostate cancer, ranging from an epidemiologic association between hypercholesterolemia and prostate cancer as well as the efficacy of statins in reducing the risk of prostate cancer, to studies illustrating dysregulation of cholesterol metabolism at the cellular level [32, 75]. It has been recently postulated that cholesteryl ester accumulation in lipid droplets within prostate cancer cells is a causative factor underlying prostate cancer aggressiveness [18]. This aberrant accumulation was demonstrated to be limited to high grade and metastatic disease, and absent from normal tissue, benign prostatic hypertrophy, prostatitis and prostatic intraepithelial neoplasia. Loss of

PTEN and subsequent activation of PI3K/Akt/mTOR with upregulation of SREBP and LDL receptors was shown to induce cholesteryl ester accumulation. This effect was independent of androgen signaling. When esterification was blocked at the level of the acetyl-coA cholesterol acyltransferase enzyme, either pharmacologically or by siRNA treatment, there was an observed increase in apoptosis accompanied by a decrease in cellular proliferation, migration and invasion both *in vitro* and *in vivo*. These data suggest the centrality of the lipid droplet to regulation of lipid metabolism in cancer. Fatty acids and cholesterol needed to support malignant growth and metastases can be accumulated and stored in these vesicles, and their subsequent mobilization as needed regulated by the phosphorylation state of the perilipin proteins that associate with the lipid droplet membrane.

Summary

The prostate appears uniquely adapted to exploit fatty acid metabolic pathways in support of malignant transformation. The protein changes observed in fatty acid metabolic pathway enzymes could be utilized as biomarkers for prostate cancer diagnosis and prognosis as well as novel targets for treatment. AMACR is now widely used as a biomarker for prostate cancer diagnosis [76, 77]. To date, limited efforts to utilize alterations in lipid metabolism to halt uncontrolled growth and metastases have been unproductive, but as evidenced in this review, there are many additional areas to explore as potential targets for treatment. ACSL4 expression, for example, is associated with an aggressive phenotype, while ACSL3 expression is regulated by androgens. Isoform specific inhibitors of either or both these enzymes might abrogate the lipogenic advantage characteristic of prostate cancer cells with minimal general toxicity. A general ACSL inhibitor, triacsin C, has already been demonstrated to be effective against solid tumors in mice [78]. With respect to fatty acid oxidation, many inhibitors are currently available for testing [69].

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Disclosure of conflict of interest

None.

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