Lipids and Prostate Cancer

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Abstract

The role of lipid metabolism has gained particular interest in prostate cancer research. A large body of literature has outlined the unique upregulation of *de novo* lipid synthesis in prostate cancer. Concordant with this lipogenic phenotype is a metabolic shift, in which cancer cells use alternative enzymes and pathways to facilitate the production of fatty acids. These newly synthesized lipids may support a number of cellular processes to promote cancer cell proliferation and survival. Hence, *de novo* lipogenesis is under intense investigation as a therapeutic target. Epidemiologic studies suggest dietary fat may also contribute to prostate cancer; however, whether dietary lipids and *de novo* synthesized lipids are differentially metabolized remains unclear. Here, we highlight the lipogenic nature of prostate cancer, especially the promotion of *de novo* lipid synthesis, and the significance of various dietary lipids in prostate cancer development and progression.

Keywords

Prostate cancer; *de novo* lipogenesis; dietary fat

Introduction

Prostate cancer is the second most common occurring cancer in men worldwide [1] and the leading site for cancer incidence in men of the United States [2]. It is estimated that every one in six men will develop prostate cancer in their lifetime [2]. With sharply increasing statistics in incidence, it is imperative that we identify major contributors to prostate cancer development and progression to recommend guidelines for prevention and treatment. One common theme in a growing body of literature is the interplay between lipid metabolism and prostate cancer. The metabolic shift from catabolic to anabolic metabolism is a hallmark of cancer cells, and many cancers, including that of the prostate, appear to require the *de novo* synthesis of fatty acids. Besides fatty acids, other lipids derived from the mevalonic acid pathway, such as cholesterol and androgens, are also strongly implicated in prostate cancer. Whether these fatty acids must be produced *de novo*, or whether they can be supplied by dietary means remains unclear; however, epidemiological studies suggest dietary fat consumption also contributes to risk of prostate cancer development and progression. In this review, we describe the lipogenic phenotype of prostate cancer, whereby cancer cells

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metabolically reprogram to promote lipid synthesis, and the contribution of various dietary fats in prostate cancer.

De Novo Lipogenesis in Prostate Cancer

Cancer cells are characterized by a large number of metabolic alterations. One major change from their normal counterpart is a shift from catabolic to anabolic metabolism. Otto Warburg first described this metabolic shift nearly a century ago [3]. The proclaimed Warburg Effect describes the unique phenomenon of aerobic glycolysis in a cancer cell, whereby cancer cells consume a large quantity of glucose, metabolize it via glycolysis, and release the majority as lactic acid into the extracellular space – most peculiarly, this occurs under normal oxygen conditions. Normally, each molecule of glucose consumed by a cell is metabolized through glycolysis to two molecules of pyruvate. Pyruvate is then converted to acetyl-CoA in the mitochondria where it enters the tricarboxylic acid (TCA) cycle to produce redox substrates for oxidative phosphorylation, the cell's major energy-producing, catabolic pathway. Interestingly, cancer cells seem to consume an excessive quantity of glucose, and utilize it both catabolically, as just described, and anabolically, whereby the carbons are used as a source to synthesize and fulfill the macromolecular demand of their proliferative phenotype. Although the production of amino acids and nucleic acids is certainly an integral characteristic of the cancer anabolic phenotype, here we describe the cancer cell's requirement for *de novo* fatty acids, and the specific use of alternative enzymes, metabolic pathways, and common oncogenic pathways to promote the synthesis of fatty acids and other lipids in prostate cancer cells.

Fatty Acid Synthesis and Prostate Cancer

Fatty acid synthesis occurs in the cytosol and begins with the production of acetyl-CoA from citrate by ATP citrate lyase (ACLY) (Figure 1). Acetyl-CoA is then converted to malonyl-CoA by acetyl-CoA carboxylase (ACACA, commonly referred as ACC1); this is the first committed and rate-limiting step of fatty acid synthesis. Fatty acid synthase (FASN) then processes one acetyl-CoA and seven malonyl-CoA molecules through a series of catalytic domains to produce palmitate, a saturated 16-carbon fatty acid. Palmitate is the primary product of FASN, representing about 80-90% of total fatty acids produced; FASN also produces myristate (14:0) and stearate (18:0) [4, 5]. Further modification may occur by other desaturase enzymes, such as stearoyl-CoA desaturase (SCD) or elongase enzymes, to insert double bonds or increase the carbon chain length, respectively, before the fatty acids are ultimately utilized for energy, protein modification, or incorporation into complex lipid structures for cellular signaling and membrane integrity.

With the exception of brain, liver, adipose and lung tissues, fatty acid synthesis in normal, differentiated adult cells is relatively low [5, 6]. Outside of these tissue types, cells may utilize circulating fatty acids derived from dietary sources to fulfill their fatty acid requirements. However, it was recognized over 50 years ago that cancer cells exhibit increased production of *de novo* fatty acids [7]. Upregulation of fatty acid synthesis in prostate cancer can arise as a consequence of a variety of events. Increased gene copy number of FASN in prostate adenocarcinoma coordinates with overexpression of FASN protein [8]. Increased transcriptional activation of FASN has been well described and is very common in prostate cancer [9-12]. Stabilization of FASN protein by ubiquitin-specific protease-2a (USP2a) has been shown to increase fatty acid synthesis in prostate cancer [13]. Loss of tumor suppressor proteins, such as PTEN and LKB1, results in prostate neoplasia and activation of AKT [14, 15], a well-described activator of FASN expression [16]. Finally, FASN itself has been postulated as an oncogene, as its overexpression in mouse prostate leads to prostatic intraepithelial neoplasia [17]. Collectively, these cellular perturbations

demonstrate that fatty acid synthesis is a unique characteristic of cancer and, hence, an attractive therapeutic target for prostate cancer.

Prostate Cancer Cells Require Fatty Acid Synthesis

In line with an altered metabolism, cancer cells shunt glucose-derived carbons from the mitochondrial TCA cycle to the cytosol to feed fatty acid synthesis. This increased influx of carbon toward fatty acid synthesis is accompanied by upregulation of the enzymes in the fatty acid synthesis pathway. The major transcriptional regulator of enzymes in this pathway is the sterol response element binding protein-1c (SREBP-1c). SREBP-1c is a lipogenic transcription factor that regulates the expression of glycolytic enzymes and fatty acid synthesis enzymes, including ACLY, ACACA, FASN, and SCD-1 [18]. Expression of SREBP-1c can be stimulated by androgens and epidermal growth factor (EGF) in prostate cancer cells [9, 10], and in turn, expression of the androgen receptor is regulated by SREBP-1c [19], creating a positive feedback loop for the expression of lipogenic enzymes. Overexpression of SREBP-1 is sufficient to increase tumorigenicity and invasion of prostate cancer cells [19]. Not surprisingly, increased expression of FASN and the lipogenic phenotype has been documented in various cancer types, including prostate [12], breast [20], ovarian [21], colorectal [22], and others (as reviewed in [23-25]). Pharmacological or small-interfering RNA-mediated inhibition of enzymes in the *de novo* fatty acid synthesis pathway, namely ACLY, FASN, or SCD-1 inhibits prostate tumor growth [26-28]. Additionally, inhibition of ACACA, FASN, or SCD-1 induces cancer cell death [11, 26-31], demonstrating the requirement for *de novo* fatty acids for prostate cancer survival.

Utility of *de novo* Fatty Acids in Prostate Cancer

Unlike their normal counterparts, cancer cells require fatty acid synthesis for growth and survival; hence, they likely utilize these *de novo* synthesized fatty acids to fulfill specific needs. Because cancer cells divide rapidly, one major purpose for increased fatty acid synthesis is to supply the heavy demand for new membrane biogenesis. In fact, Swinnen et al. [32] showed that *de novo* fatty acids used for membrane biogenesis also preferentially localize in the membrane's signaling raft domains. Membrane composition has been shown to affect the conformation and activation of membrane-bound proteins [33]; thus, *de novo* fatty acids may play a significant role in propagating oncogenic signals from the plasma membrane. Indeed, FASN regulates HER2 expression and activation of AKT [34]. Moreover, enrichment of saturated fatty acids by FASN in tumor cell membranes protects cells from lipid peroxidation and oxidative stress-induced cell death [35]. Overexpression of FASN in prostate cancer supports palmitoylation and activation of oncogenic proteins [36]. Additionally, lipid signaling ligands can be derived specifically from the *de novo* fatty acid pool [37], suggesting an absolute requirement of fatty acid synthesis to activate specific signaling pathways. Although lacking evidence of a direct role for fatty acids, FASN and ACACA are also required for cell cycle progression [31, 38]. Overall, prostate cancer cells may utilize *de novo* fatty acids for a variety of uses, all of which facilitate proliferation and survival of cancer cells.

Prostate Cancer Metabolism Favors Fatty Acid Synthesis

Fatty acid synthesis is an extremely demanding process; it requires 8 citrate, 8 ATP, and 14 NADPH molecules to produce just a single palmitate molecule. Excessive fatty acid synthesis appears to be a requirement for prostate cancer growth and survival; thus, cancer cells have adapted the use of alternative metabolic pathways and enzymes to provide the necessary substrates for lipogenesis and prevent its inhibition by upstream signaling mediators. These alternative pathways include isoform switching, truncation of the TCA cycle and the use of TCA cycle intermediates for fatty acid synthesis, and the increased use

of other non-canonical metabolic enzymes, such as the pentose phosphate pathway and cytosolic TCA cycle enzymes (Figure 1).

Metabolism for fatty acid synthesis ultimately begins with cellular uptake of glucose. Cancer cells consume a large quantity of glucose as their major energy source. Upon entering a cell, glucose is phosphorylated by hexokinase (HK) to glucose-6-phosphate (G6P). Humans possess four isozymes of HK1-4 and most cell types express HK1 as the housekeeping enzyme for normal catabolic metabolism of glucose [39]. However, cancer cells seem to preferentially express HK2, which is thought to support anabolic metabolism [40]. Prostate cancer cells strongly upregulate HK2 and lipid synthesis in response to androgen [41]. G6P, produced by HK2, may take one of two fates: metabolism by the pentose phosphate pathway (PPP) or glycolysis. Cancer cells can shunt G6P through the PPP to produce NADPH, which is a critical reductant for fatty acid synthase. PPP intermediates can also return to glycolysis, producing pyruvate, which may be used later for fatty acid synthesis.

Tumor cells preferentially express the embryonic isoform of pyruvate kinase (PKM2), the terminal enzyme of glycolysis. Compared to PKM1, the splice variant found in most adult tissues, PKM2 is characterized by a weaker substrate affinity and decreased activity [42, 43]. Insights to the advantages of which PKM2 imposes on cancer cells have surfaced only recently. Studies by Cantley and colleagues have shown PKM2 promotes tumor growth and survival by maintaining a high glycolytic rate, low oxidative phosphorylation, and redox homeostasis [44, 45]. Expression of PKM2 in prostate cancer was also shown to be associated with an alternative mechanism of producing pyruvate in the absence of ATP production [46]. This suggests expression of PKM2 in prostate cancer cells promotes anabolic metabolism, such as fatty acid synthesis, by allowing high glucose consumption as a carbon source for fatty acids, but without inducing ATP-mediated inhibition of glycolysis [46].

Typically, glucose-derived citrate is processed through the mitochondrial TCA cycle to produce intermediates for oxidative phosphorylation. In contrast, cancer cells shunt citrate from the TCA cycle to the cytoplasm and use alternative methods to metabolize citrate that promote fatty acid synthesis. Cytosolic citrate can be converted to isocitrate by cytosolic aconitase (ACO1), and subsequently to α-ketoglutarate by cytosolic isocitrate dehydrogenase (IDH1); the latter reaction produces additional NADPH for fatty acid synthesis. Overexpression of IDH1 in male mice leads to significantly increased epididymal fat weight and adipogenesis, coinciding with hyperlipidemia and obesity [47]. Interestingly, oncogenic mutations in *IDH* have been characterized in several cancer types [48, 49]. These findings suggest IDH1 plays a significant role promoting fatty acid synthesis and lipid metabolism in cancer.

Cytosolic citrate, in addition to being metabolized outside of the TCA cycle to produce NADPH, can also be converted to acetyl-CoA by ACLY, and can be used for both fatty acid and sterol synthesis. A byproduct of this reaction is oxaloacetate, which is converted to malate by malate dehydrogenase. Cytosolic malate may be converted back to pyruvate by cytosolic malic enzyme (ME1) to produce yet more NADPH, or it can be recycled back to the mitochondria by the citrate transport protein in the mitochondrial membrane, which coordinates the influx of cytosolic malate with the efflux of mitochondrial citrate [50], completing a loop for driving mitochondrial carbon sources toward fatty acid synthesis. Prostate tissue is unique in its transport system of citrate in that normal prostate cells produce large amounts of intracellular citrate and release it into the prostatic fluid [51], where it can act as an energy source for sperm [52]. Prostate cancer cells, however, have significantly decreased intracellular citrate levels. This is accompanied by increased c-ACNT expression and activity [53] and increased ACLY [27]. Collectively, these findings

suggest that prostate cancer cells rapidly utilize citrate for lipogenesis, either to produce NADPH or shunt as a carbon source for fatty acid production.

Although *de novo* synthesized fatty acids are typically derived from glucose, some cancer cells rely on glutamine metabolism. Because glucose carbons are shunted from the mitochondria for fatty acid synthesis, prostate cancer cells convert glutamine to α-ketoglutarate and shuttle it into the mitochondria to replenish TCA cycle intermediates for anaplerotic reactions [54, 55]. Additionally, cancer cells experiencing selective pressure by hypoxia, or a defective electron transport chain, use glutamine, rather than glucose, as the major lipid precursor. In such a scenario, stabilized HIF-1α inhibits the conversion of pyruvate to acetyl-CoA, and IDH1 and ACO1 work in reverse to convert α-ketoglutarate to citrate, which is then metabolized by ACLY for lipid synthesis [56, 57] (Figure 1).

Oncogenic Signaling Pathways Promote Fatty Acid Synthesis

Further demonstrating the importance of fatty acid synthesis in prostate cancer, some of the major disease-driving signaling pathways regulate the expression of lipogenic enzymes. As a lipid phosphatase, PTEN opposes the action of PI3K by removing a phosphate group from phosphatidylinositol-3,4,5-triphosphate, an essential activator of AKT [58]. Loss of *PTEN*, is one of the most common events observed in prostate cancer, occurring in approximately 40% of primary cancers and over 70% of castration resistant and metastatic prostate cancers [59-62]. *Pten* deletion leads to invasive prostatic adenocarcinoma in mice [14], and induces expression of FASN [63]. Treatment with a PI3K inhibitor or reintroduction of *PTEN* in PTEN-null prostate cancer cells reduces FASN expression [63]. Conversely, inhibition of FASN reduces expression and activation of AKT [64], which was recently shown to occur by increased degradation of AKT and its downstream effectors [65]. Additionally, cell growth inhibition by inhibiting FASN can be overcome by hyperactivation of AKT [65]. Collectively, these studies strongly suggest coordinate feedback between lipogenesis and PTEN/PI3K/AKT oncogenic signaling to promote cancer growth and tumor progression.

HER2 is a well-recognized oncogene and diagnostic marker in multiple cancers [66]. Overexpression of HER2 in the absence of amplification has been identified in approximately 20% of prostate cancers, and significantly associates with high Gleason grade, proliferation, and tumor recurrence [67]. It activates fatty acid synthesis via activation of the PI3K/AKT signaling pathway [68]. Surprisingly, HER2 regulation of fatty acid synthesis does not occur transcriptionally via SREBP-1c, but rather, translationally through activation of mTOR and increased FASN protein [69]. Inhibition of FASN attenuates HER2 oncogenic signaling and downregulates activation of AKT and ERK1/2 [34].

A number of studies have linked oxidative stress to prostate cancer development and progression [70-73]. Hypoxia, a common feature of tumors characterized by lack of blood supply, and consequently, nutrients and oxygen to the growing tumor, can lead to oxidative stress. Furuta and colleagues [74] demonstrate that a hypoxic environment or treatment with hydrogen peroxide induces AKT/HIF-1α-mediated activation of SREBP-1, which increases transcription of FASN. SREBP-1 can also increase expression of NOX5 [19], a prominent producer of ROS and regulator of prostate cancer cell growth [75], suggesting another feed forward mechanism inducing lipogenesis and prostate cancer growth.

Androgen signaling is a major driver of prostate cancer, and androgen ablation is a primary therapeutic strategy for prostate cancer patients. Activation of the androgen receptor (AR) by androgen increases expression of lipogenic enzymes in a SREBP-1c-dependent manner [9, 10], and a positive feedback loop promotes this signaling pathway since binding sites for SREBP-1 transcription factors are also found in the AR gene of prostate cancer cells [19]. AR is regulated by β2-microglobulin (β2-M), a component of the housekeeping major

histocompatibility complex class I molecule found on prostate cancer cells, in a MAPK/ SREBP-1-dependent manner. Inhibition of β2-M by a selective antibody decreases the interaction between SREBP-1 and its binding site in the AR promoter region, resulting in decreased AR expression and lipogenesis by FASN [76]. A new AR splice variant, AR8, was recently identified and is strongly expressed in castration resistant prostate cancer (CRPC). AR8 is found at the plasma membrane where it associates with EGFR and induces nuclear translocation of AR in response to EGF [77]. Because we know AR activates FASN [10], this may partly explain how EGF activates FASN [9], and provides a mechanism for activation of AR signaling in CRPC. AR8 also requires FASN for functionality, as palmitoylation appears to tether it to the membrane [77]. Whether AR8 activates SREBP-1 is unknown. Interestingly, inhibition of SREBP-1, ACACA, FASN, or SCD-1 results in decreased AR expression and activity [19, 78, 79]. Concomitant overexpression of AR and FASN in prostate is sufficient to induce adenocarcinoma in mice [17]. Overall, these results suggest androgen signaling is strongly associated with activation of fatty acid synthesis and conversely, fatty acid synthesis promotes androgen signaling. Together these signaling pathways may work in concert with other major oncogenic signaling pathways to promote prostate cancer development and progression.

Cholesterol and Steroid Synthesis in Prostate Cancer

De novo steroids are produced from cholesterol, which is synthesized by the mevalonic acid pathway (Figure 1). Transcriptional regulation of the enzymes in this pathway occurs through activation of the sterol response element binding protein-2 transcription factor (SREBP-2) [80]. SREBP-2, a regulator of androgen synthesis, is also itself regulated by androgens [80], demonstrating a direct feedback circuit for regulation of androgen production. Interestingly, SREBP-2 expression increases during disease progression and is significantly higher after castration [81]. The transcription factor also lacks its feedback inhibition in prostate cancer cells [82], overall, implicating a role for cholesterol and androgen synthesis in prostate cancer.

Major biological functions of the lipid molecules produced by the mevalonic acid pathway include post-translational modification, lipid raft formation, and steroid synthesis, all of which influence prostate cancer development and progression [83, 84]. Statin drugs were designed to inhibit HMG-CoA reductase, the rate-limiting enzyme of cholesterol synthesis, and were originally indicated for the treatment of cardiovascular disease; however, long term use of statin drugs has shown beneficial effects in reducing prostate cancer risk [85, 86]. Therefore, much research has focused on possible mechanisms of statin-mediated inhibition of prostate cancer (reviewed in [87-90].

During the synthesis of cholesterol, the mevalonate pathway produces several metabolic intermediates used as protein modifiers, such as isoprenoids, geranylgeranyl pyrophosphate, and farnesyl pyrophosphate [83]. These protein modifiers can prenylate oncogenic proteins such as Ras and Rho, which can regulate proliferation, migration, and invasion of prostate cancer cells [88]. Cholesterol itself can post-translationally modify cancer promoting proteins, such as sonic hedgehog [91], promoting dedifferentiation and facilitating cancer growth and metastasis [92]. Cholesterol is also a major component of plasma membrane lipid raft microdomains, which mediate formation of oncogenic protein signaling complexes [93], including that of the PI3K/AKT pathway. The cholesterol binding protein caveolin-1 has been implicated as a promoter of prostate cancer, as its deletion in the TRAMP prostate cancer mouse model decreased tumor growth and slowed histopathological progression [94]. Hence, inhibition of the mevalonic acid pathway may reduce prostate cancer growth and progression through several lipid signaling mechanisms. Although, statin-mediated inhibition of prostate cancer has also been suggested to occur through other mechanisms, such as anti-angiogenic and anti-inflammatory effects [95].

A common therapy for advance prostate cancer patients involves deprivation of androgens by surgical or medical castration, resulting in decreased circulating androgens and prostate tumor shrinkage. However, despite these initial responses, essentially all patients experience relapse and progression to castration resistant disease and metastasis. Formerly described as androgen independent, it is now well recognized that castration resistant prostate cancer (CRPC), including bone metastases, express AR and maintain an active androgen signaling pathway [96, 97]. New evidence has emerged to suggest prostate cancer cells produce androgen themselves, thereby propagating the androgen signaling pathway, even after androgen deprivation therapy [98, 99]. Increased cholesterol concentration was identified in prostate cancer bone metastases [100], along with increased expression of enzymes involved in steroidogenesis [101, 102]. Studies suggest these intratumoral androgens may be derived from *de novo* synthesized cholesterol of the mevalonic acid pathway [102], as well as circulating cholesterol from the diet [103]. Recall that androgens, via activation of AR, stimulate activation of the *de novo* fatty acid synthesis pathway [10]. Therefore, after androgen deprivation therapy prostate cancers likely increase their steroid synthesis from circulating and *de novo* synthesized cholesterol as a means to amplify activation of fatty acid synthesis and encourage progression to castration resistance.

Clinical Implications for Lipogenesis and Prostate Cancer

Expression and activation of the fatty acid synthesis and mevalonic acid pathways is clearly an integral component of prostate cancer as a disease. Hence, a number of studies have attempted to exploit the lipogenic phenotype, by chemical inhibition of lipogenic enzymes as a means to treat cancer [26, 27, 31, 104-109]. Because cancer cells depend on FASN for tumor growth and survival, pharmacological inhibition of FASN is an attractive approach, especially considering that inhibition of FASN does not appear to affect normal prostate cells [32]. Unfortunately, such attempts have not yet yielded fruitful results, as inhibitors are either too insoluble and have low bioavailability due to the hydrophobic properties of the FASN active site [28, 110], or alter eating habits in mice by inactivation of hypothalamic AMPK, ultimately leading to rapid weight loss and anorexia [111].

Although FASN is an ideal target due to the numerous metabolic alterations that converge on this enzyme, inhibition of other enzymes in the fatty acid synthesis pathway may be an alternative approach. Soraphen A, an inhibitor of ACACA, possesses anti-lipogenic and anti-tumorigenic properties; however, similar to FASN inhibitors [112], it is non-selective and activates fatty acid oxidation, while concomitantly inhibiting fatty acid synthesis [31]. Other drugs, such as SB-204990 and BZ36, which target ACLY and SCD-1, respectively, have demonstrated efficacy in animal models [26, 31], but also have not advanced to clinical trials.

Studies suggest dysregulation of glucose and lipid metabolism, components of a disease described as metabolic syndrome, strongly associate with cancer incidence and aggressiveness [113, 114]. Even the transcriptional signatures and molecular properties of cancer and metabolic syndrome display significant overlap [115]. Hence, it should be no surprise that common drug treatments for metabolic disease, especially cholesterol lowering statin drugs, have shown efficacy in regulating cancer [85, 90, 116]. In fact, a search for active studies on "statin" intervention in "cancer" conditions identifies 36 different clinical trials investigating the adjuvant or prophylactic therapeutic value of statin drug use in various cancers (clinicaltrials.gov). Another well described culprit of metabolic disease is the 5′-AMP-activated protein kinase (AMPK) [117-119]. AMPK acts as an energy sensor by monitoring the ratio of AMP to ATP. At high concentrations of AMP, AMPK is activated by phosphorylation and begins to shut down ATP consuming processes, including fatty acid synthesis and sterol synthesis, and activates energy producing pathways to maintain energy homeostasis. AMPK directly inhibits ACACA, HMG-CoA reductase, and SREBP-1,

making it an attractive target for inhibiting lipogenesis in prostate cancer (reviewed in [120]). Several small molecules and natural products have been shown to either directly or indirectly activate AMPK, including Metformin, a well-recognized and approved treatment for type II diabetes. Metformin and other natural products known to activate AMPK are currently being tested in clinical trials to determine their efficacy in treating various cancers (reviewed in [121]).

Despite complications of inhibitor development, lipogenesis in prostate cancer can be exploited for prostate cancer diagnosis as well. Detection of FASN in prostate is an early diagnostic marker and indicator of disease progression [12, 122]. Both SREBP-1c and FASN staining correlate with high Gleason grade [12, 16, 122]. Expression of FASN may complement the current AMACR staining to distinguish questionable cases during diagnosis [123]. Radiolabeled substrates of fatty acid precursors, such as 1-^{11}C-acetate and 4-^{18}F-fluoro-L-glutamic acid, also carry diagnostic value for cancer patients [124, 125]. Radiolabeled ^{11}C-acetate displayed less background noise and proved more efficient over the standard ^{18}F-fluorodeoxyglucose in diagnostic PET imaging for prostate cancer patients [125-127]; although, a very recent study reported complications in distinguishing benign hyperplasia and prostate cancer [128]. A clinical trial for 4-^{18}F-fluoro-L-glutamic acid as a metabolic substrate was also recently completed (NCT00961831); results are pending.

Dietary Lipids and Prostate Cancer

Epidemiological studies show that prostate cancer is associated with obesity and increased body mass index [129-131], and research suggests that a diet low in fat decreases risk of prostate cancer development and progression [132-138]; however, some studies argue dietary fat is not associated with cancer risk [139, 140]. Diets around the globe vary in their total fat content, as well as their enrichment for specific lipids, which may contain varying quantities of saturated fatty acid (SAFA), monounsaturated fatty acid (MUFA), and polyunsaturated fatty acid (PUFA). These epidemiological studies correlating regional diets and risk of prostate cancer development have initiated a surge of research investigating the role of various types of dietary lipids in prostate cancer. Unfortunately, a large majority of epidemiology studies rely on patient questionnaires to assess the implications of diet in prostate cancer, and can often inaccurately reflect the patient's true diet [141]. Many preclinical studies have attempted to ameliorate this inaccuracy and identify the dietary components affecting prostate cancer development and progression by formulating controlled diets in animal models; however, even preclinical studies remain controversial in their findings. A confounding factor between many preclinical studies is the variance in dietary formulation, specifically the source of dietary fat and the quantity of specific types of SAFA, MUFA, and PUFA, and especially their ratio to the respective control diet. Additionally, it can be difficult to distinguish whether the type of dietary fat or simply the quantity of fat consumed is the underlying culprit of disease. While the significance of diet was proposed long ago, only recently has literature attempted to discriminate molecular mechanisms and specific types of dietary fat that may contribute to prostate tumorigenesis and progression.

Saturated Fatty Acids

Common dietary sources rich in SAFA include animal meat, milk, eggs, palm oil, and coconut oil. The most prevalent species of dietary SAFA are palmitic acid (16:0) and stearic acid (18:0), although some foods, such as coconut oil, are rich in short chain SAFA such as lauric acid (12:0) and myristic acid (14:0) [142]. Several epidemiological studies have suggested increased consumption of SAFA correlates with increased risk of prostate cancer and reduced progression-free survival [143-145]; however others report no significant association [146, 147].

Although a prospective study in men suggests both short- and long-chain SAFA have similar negative effects on prostate cancer risk [148], preclinical data suggests short-chain SAFA may have a beneficial effect on prostate cancer [149]. A study in rats showed that coconut oil, which is rich in lauric acid, compared to sunflower oil, which is rich in linoleic acid (18:2, n-6), can prevent prostate hyperplasia [149]. As previously mentioned, a major difficulty in assessing dietary effects of fat is identifying a reasonable control. Arguably, this effect of a coconut oil diet may not necessarily be associated with the increased short-chain SAFA consumption, but could be due to the decreased consumption of linoleic acid.

Only a few preclinical animal studies have investigated the role of dietary saturated fat in prostate cancer, and results are controversial. Some studies suggest a diet high in saturated fat does not increase prostate tumor growth or survival in mice [140]; however, others argue the opposite. Escobar et al [150] elegantly demonstrated that the quality of dietary fat, rather than quantity, could regulate prostate growth and proliferation. When comparing isocaloric diets of only 7% fat, rats on a lard-derived diet displayed significantly increased prostate weight, testosterone, cell proliferation, and expression of androgen receptor compared to rats on a linseed oil-derived diet, which is rich in α-linolenic acid (18:3, n-3) [150]. These results suggest lard, which is rich in palmitic acid and oleic acid, may have cancer-promoting effects compared to an omega-3 PUFA enriched diet.

A study by Tamura et al. [151] demonstrated a role for a novel elongase of very long chain SAFA, ELOVL7, whose expression was found to be upregulated in prostate cancer. Overexpression of ELOVL7 supplemented with a high fat diet composed of beef fat increased tumor growth and testosterone production in mouse prostate tumor xenografts. Conversely, knockdown of ELOVL7 significantly decreased 20:0 and 22:0 SAFA, but not long chain MUFA or PUFA, in phospholipids and cholesterol esters in prostate cancer cells. These data suggest prostate cancer cells use SAFA, the most abundant fatty acid found in animal fat, as substrates for membrane and androgen production to drive tumor growth. Surprisingly, a study characterizing the kinetics and substrate specificity of purified ELOVL7 showed preferential activity toward carbon chains of 16-20 in length, regardless of the presence of double bonds, with the greatest activity for 18:3 (n-3) and 18:3 (n-6) fatty acids [152]. These results confound the data observed in prostate cancer cells, suggesting perhaps ELOVL7 knockdown was compensated by another ELOVL enzyme. If so, ELOVL5 may be suspect as it is the only other ELOVL enzyme previously implicated in prostate cancer and is strongly increased in response to androgen [153].

It is important to note that saturated fatty acids may be acquired through diet and produced *de novo* by fatty acid synthesis. Several studies have demonstrated that cell death induced by FASN inhibition in cell culture can be rescued by addition of palmitic acid, the primary product of FASN [17, 29, 30]. To date, no study has described a phenotypic rescue of FASN inhibition by dietary fatty acids in a cancer animal model. However, several non-cancer models have shown that a high-fat diet is unable to rescue the effects of FASN inhibition in liver and brain [37, 154, 155]. It is possible that the cellular pools of dietary and *de novo* fatty acids distinctly supply different cellular processes, or perhaps that prostate cancer cells, which require fatty acid synthesis for survival, are fulfilling a high demand for fatty acids that simply cannot be met by the diet. Considering the appeal of fatty acid synthesis inhibition as a cancer therapeutic strategy, it would be interesting to determine whether a high-fat diet could negate this therapeutic approach.

Monounsaturated Fatty Acids

Early epidemiological studies have highlighted a lower incidence of certain cancers in Mediterranean regions [156]. A plausible cause of such a statistic is the olive oil-enriched diet of Mediterranean dwellers. The main fatty acid constituent of olive oil is oleic acid, an

18-carbon, delta-9 MUFA (18:1, n-9). Other foods rich in oleic acid include almond oil, hazelnut oil, and safflower oil [142]. Despite these early findings, effects of dietary MUFA, particularly oleic acid, on prostate cancer risk remain especially controversial. Some studies suggest a protective effect of MUFA in cancer development [157], while others describe no association between MUFA and prostate cancer [144, 147]. What is more, some studies have described a cancer promoting effect of MUFA in humans and mice [132, 158]. Because the Mediterranean diet consists of other nutrients suspected to affect cancer risk, such as tomatoes and lycopene, resveratrol, high fish and low red meat consumption, all of which may influence the development of prostate cancer [159], it is difficult to distinguish whether one or a combination of dietary factors are contributing to the observed decrease in cancer incidence. Further investigation is required to determine a more precise role, if any, for dietary MUFA in prostate cancer.

Similar to the conundrum between dietary SAFA and *de novo* SAFA, dietary MUFA and *de novo* MUFA may also have distinct roles in prostate cancer. While the effects of dietary MUFA remain quite a mystery, two studies have highlighted a role for SCD-1, the enzyme responsible for *de novo* MUFA synthesis, in the promotion of prostate cancer [26, 78]. While these studies describe the role of MUFA in the *de novo* lipogenesis pathway of cancer, no study has investigated the interplay between dietary fat and SCD-1 in prostate cancer.

Polyunsaturated Fatty Acids

In contrast to SAFA and MUFA, the two main types of PUFA, omega-6 (n-6) and omega-3 (n-3), cannot be synthesized *de novo* in mammals and are therefore acquired through the diet. Linoleic acid (LA, 18:2, n-6) is the most common dietary omega-6 PUFA and can be converted to arachidonic acid (AA, 20:4, n-6), which is a precursor to many different eicosanoids [160]. LA is enriched in certain oils such as that of corn, sunflower, and safflower [142]. α-Linolenic acid (α-LNA, 18:3, n-3) is the major precursor to long-chain omega-3 PUFA but its conversion is limited [161]. Therefore, omega-3 derived eicosanoids are primarily derived from dietary eicosapentaenoic acid (EPA, 20:5, n-3) and docosanoids from docosahexaenoic acid (DHA, 22:6, n-3). Although largely unclear, multiple mechanisms by which PUFA exert their effects in prostate cancer have been postulated. These include processes such as eicosanoid synthesis, angiogenesis, immune cell regulation, and membrane structure and function (reviewed [160, 162]).

It is generally understood that omega-6 PUFA increase prostate cancer risk and disease progression while omega-3 PUFA show a unique, protective effect (reviewed in [160, 163]). A notable exception to this general rule is dihomo-γ-linolenic acid (DGLA 20:3, n-6). DGLA is a metabolite produced from desaturation and elongation of LA. DGLA has been shown to possess anti-tumorigenic affects due to its conversion to the anti-inflammatory 1-series and 3-series of eicosanoids by cyclooxygenase and lipoxygenase enzymes, respectively (reviewed in [164]). Perhaps because the conversion of DGLA to AA is a relatively inefficient reaction [165], DGLA does not produce the same pro-tumorigenic results as AA. A recent publication suggests the anti-tumorigenic effects of DGLA are due to its ability to directly inhibit FASN. Work by Zhang et al. [166] depicted the crystal structure of DGLA bound to the thioesterase domain of FASN, consequently inhibiting fatty acid synthesis and inducing cancer cell death.

While the subject of good versus bad PUFA is still debated, no study has refuted the benefits of a balanced PUFA diet. In support of epidemiological data [167], several animal studies have described an anticancer benefit from diet containing a low omega-6 to omega-3 ratio [137, 168-170], which is in contrast to the high 30:1 ratio of the standard Western diet.

Overall, literature seems to suggest dietary PUFA likely modulate prostate cancer biology; however, its molecular mechanisms warrant further investigations.

Conclusions

Both *de novo* and dietary lipids seem to be important contributors to prostate cancer growth and development. Cancer cells themselves have adjusted their metabolic priorities toward the synthesis of macromolecules, especially lipids for membrane biogenesis and signaling molecules, as an apparent means to fulfill their demanding proliferation rate. Even more peculiar, however, is their absolute dependence on fatty acid synthesis for survival, highlighting an attractive metabolic addiction that may be exploited at multiple molecular targets by cancer therapeutics. It remains uncertain whether cancer cells differentially utilize *de novo* lipids and dietary lipids. Although significant evidence from epidemiology and preclinical animal studies suggests dietary fat consumption affects prostate tumorigenesis and cancer progression, no study has effectively determined whether diet could potentially negate therapeutic efforts targeting cancer cell lipogenesis. Overall, a diet balanced in fat consumption may reduce the risk of prostate cancer development and prevent disease progression.

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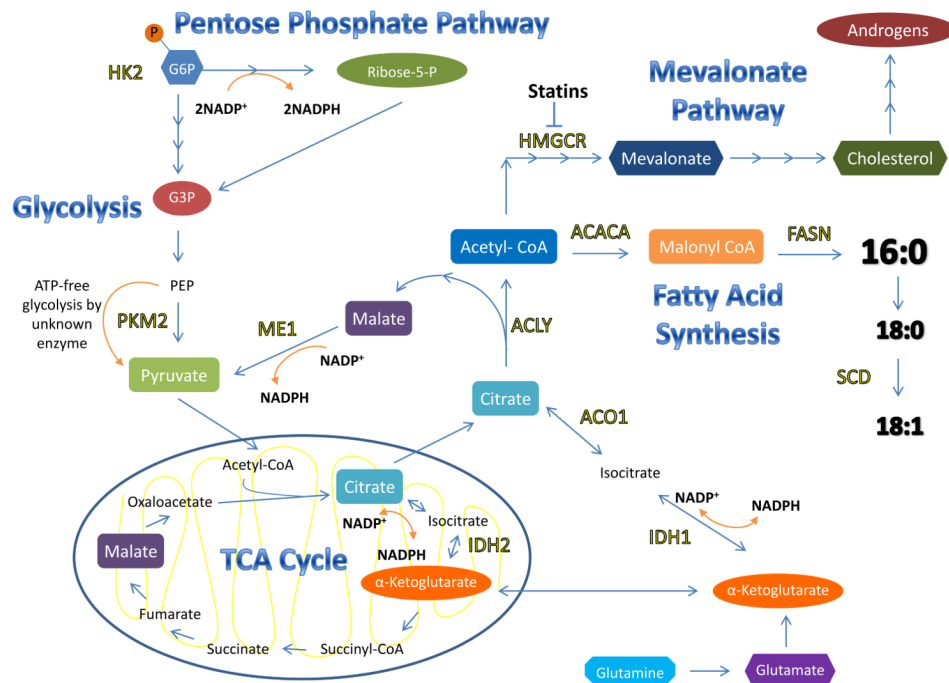
Figure 1. Cancer Cell Metabolism Promotes Fatty Acid Synthesis
Glucose entering the cell is immediately phosphorylated by Hexokinase 2 (HK2), producing glucose-6-phosphate (G6P). G6P can enter both glycolysis and the pentose phosphate pathway (PPP). Expression of pyruvate kinase M2 (PKM2) promotes the ATP-free conversion of phosphoenolpyruvate (PEP) to pyruvate by a currently unknown enzyme, which may prevent ATP-mediated inhibition of glycolysis. Citrate is exported from the mitochondrial TCA cycle to fuel the fatty acid synthesis pathway by conversion to acetyl-CoA by ATP citrate lyase (ACLY). Acetyl-CoA carboxylase 1 (ACACA) initiates the first committed step to fatty acid synthesis to produce malonyl-CoA. Seven malonyl-CoA molecules are added to acetyl-CoA by fatty acid synthase (FASN) to produce palmitic acid (16:0). Palmitic acid can be further elongated to stearic acid (18:0) and desaturated by stearoyl-CoA desaturase (SCD) to produce oleic acid (18:1). Citrate may also be recycled to produce NADPH for fatty acid synthesis by malic enzyme (ME1), which produces pyruvate, or by cytosolic aconitase (ACO1) followed by cytosolic isocitrate dehydrogenase (IDH1) to produce α-ketoglutarate. Glutamine can be converted to α-ketoglutarate upon entering the cell, to replenish TCA cycle intermediates or fuel fatty acid synthesis. The reduced form of nicotinamide adenine dinucleotide phosphate (NADPH), a critical reductant for fatty acid synthase (FASN), is produced from the activity of the PPP, ME1, and IDH.