New insights into lipid metabolism and prostate cancer (Review)

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Received February 7, 2023; Accepted May 5, 2023

DOI: 10.3892/ijo.2023.5522

Abstract. Prostate cancer (PCa) is the most common malignant tumor of the male urological system and poses a severe threat to the survival of middle-aged and elderly males worldwide. The development and progression of PCa are affected by a variety of biological processes, including proliferation, apoptosis, migration, invasion and the maintenance of membrane homeostasis of PCa cells. The present review summarizes recent research advances in lipid (fatty acid, cholesterol and phospholipid) metabolic pathways in PCa. In the first section, the metabolism of fatty acids is highlighted, from formation to catabolism and associated proteins. Subsequently, the role of cholesterol in the pathogenesis and evolution of PCa is described in detail. Finally, the different types of phospholipids and their association with PCa progression is also discussed. In addition to the impact of key proteins of lipid metabolism on PCa growth, metastasis and drug resistance, the present review also summarizes the clinical value of fatty acids, cholesterol and phospholipids, as diagnostic and prognostic indicators and therapeutic targets in PCa.

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Abbreviations: ACLY, ATP citrate lyase; ACC, acetyl-CoA carboxylase; AR, androgen receptor; ACAT, acyl coenzyme A-cholesterol acyltransferase; ACSL3, acyl-CoA synthetase long chain family member 3; ANX, annexin; CRPC, castration-resistant prostate cancer; Ca^{2+}, calcium; CPT1, carnitine palmitoyl transferase 1; CEs, cholesteryl esters; DHT, dihydrotestosterone; DECR1, 2,4-dienoyl-CoA reductase 1; ELOVL, elongation of very-long-chain fatty acids protein; FASN, fatty acid synthase; FABPs, fatty acid-binding proteins; HOX, homeobox; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LDLr, low-density lipoprotein receptor; PCa, prostate cancer; PPAT, periprostatic adipose tissue; PSA, prostate-specific antigen; PPARγ, peroxisome proliferator-activated receptor γ; PNB, prostate needle biopsy; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PI, phosphatidylinositol; PS, phosphatidylserine; PIN, prostatic intraepithelial neoplasia; SCD, stearoyl-CoA desaturase; SREBPs, sterol regulatory element binding proteins; SR-B1, scavenger receptor class B type 1; SQLE, squalene epoxidase/monooxygenase; SM, sphingomyelin; TME, tumor microenvironment; VEGF, vascular endothelial growth factor

Key words: prostate cancer, lipid metabolism, fatty acids, cholesterol, phospholipid

Contents

1. Introduction

According to recent statistics, prostate cancer (PCa) continues to have a high incidence, and it is the most prevalent type of cancer among adult males in developed nations; it is also associated with the second-highest rate of cancer-related mortality among males, and poses a significant global public health burden (1). Age, race and a family history of the disease have been identified as the main risk factors for PCa (2). Studies have demonstrated that a high-fat diet is a preventable factor linked to disease progression (3).

In tumorigenesis and progression, in addition to genetic mutations, epigenetic alterations and altered cellular signaling pathways, tumor cells spontaneously generate metabolic reprogramming, which is also a key feature that distinguishes them from normal tissues (4,5). In 2017, Flavahan *et al* (6) introduced the notion of energy metabolic reprogramming, which includes three primary abnormal metabolic pathways: Sugar, lipid and amino acid metabolism. The Warburg effect is the lack of typical oxidative phosphorylation in the mitochondria, and tumor cells continue to generate energy mostly through anaerobic glycolysis, even in an environment with abundant oxygen. The Warburg effect is the biological enhancement

of tumor cell proliferation, migration and invasion caused by the absence of typical oxidative phosphorylation in the mitochondria (7). Fatty acid metabolism plays a crucial role in maintaining membrane structure formation, the post-translational modification of oncoproteins, energy storage and supply, and signaling in tumor cells; it is also closely linked to the onset, progression, drug resistance and recurrent metastasis of PCa. Lipid metabolism is one of the main energy sources of tumor cells.

It has been established that obesity is a risk factor for the development of PCa in the genetic context of phosphatase and tensin homolog (PTEN) (8) deficiency and that a high-fat diet causes lipid buildup that is sufficient to promote metastasis (9). The prostate is surrounded by periprostatic adipose tissue (PPAT), whose adipocytes secrete the chemokine, CCL7. This chemokine moves from PPAT to the periprostatic region and promotes the migration of tumor cells that express CCR3 (10). PCa has an active lipophagy mechanism (11). Additionally, PCa exhibits a number of abnormalities in lipid metabolism, including the increased uptake of circulating lipids (12), the increased *ab initio* synthesis of fatty acids and phospholipids (13), the increased transfer of fatty acids from stromal adipocytes into PCa cells (14), and increased phospholipids (15) in contrast to cholesterol stored in cytoplasmic lipid droplets as cholesterol esters (16).

In general, lipid metabolism is closely related to the pathogenesis and progression of PCa, and its molecular mechanisms and signaling pathways are relatively complex. the present review focuses on certain new proteins that regulate lipid metabolism and discusses the relevance of fatty acid, cholesterol and phospholipid metabolic processes to PCa, as well as the clinical application values of these novel markers in the diagnosis and prognosis of PCa. The present review aims to lay the foundation for subsequent studies on the role and mechanisms of lipid metabolism in human cancer.

2. Fatty acid metabolism in prostate cancer

Sources of fatty acids

Exogenous fatty acids. Fatty acid metabolism is a critical part of lipid metabolism. The altered metabolic activity of fatty acids can contribute to the malignant properties of cancer cells (17). Some fatty acids are produced by adipose tissue lipolysis or triglyceride breakdown in circulating chymotrypsin and lipoproteins. These exogenous fatty acids are the preferred source of adenosine 5'-triphosphate production, membrane biosynthesis, energy storage and the production of a wide range of signaling molecules in the majority of non-tumor cells (Fig. 1) (18).

Adipose-derived fatty acids are also strongly linked to cancer, and when adipocytes are located near tumor lesions, their secretory products can influence disease progression, as observed in ovarian and breast cancers (19,20). The prostate is surrounded by PPAT, which provides a high concentration of fatty acids and alters the prostate tumor microenvironment (TME) (11). Lipoproteins in the TME can also be taken up by cancer cells, providing them with cholesterol and fatty acids (21). In PCa cells, fatty acid uptake increases and serves as a direct raw material for substance production. CD36 has been described as a carrier that mediates fatty acid transport. It has been shown that CD36 knockdown in cancer-susceptible *PTEN*$^{-/-}$ mice reduces fatty acid uptake and the lipid abundance of oncogenic signals, thereby inhibiting tumor progression (22). These data suggest that the inhibition of fatty acid uptake may be a promising therapeutic approach for the treatment of PCa.

Endogenous fatty acids. The *de novo* production of fatty acids is another key source of fatty acids. Beginning with citrate, ATP citrate lyase (ACLY) catalyzes the production of acetyl-CoA, which is then converted to malonyl-CoA by acetyl-CoA carboxylase (ACC) in the *ab initio* synthesis process (23). Fatty acid synthase (FASN) transforms malonyl-CoA into the 16-carbon fatty acid, palmitate. Stearoyl-CoA desaturase (SCD) then transforms palmitate into monounsaturated fatty acids. These monounsaturated fatty acids are then converted into polyunsaturated fatty acids by the action of enzymes, such as the elongation of very-long-chain fatty acid protein (ELOVL), which results in triacylglycerols (Fig. 1) (23).

Proteins associated with fatty acid metabolism

ACLY. ACLY is the first rate-limiting enzyme in the *ab initio* fatty acid synthesis pathway, catalyzing the synthesis of acetyl-CoA from citric acid. ACLY overexpression has been linked to a number of types of cancer, including lung cancer, cervical cancer, prostate cancer and osteosarcoma (24). A recent study found that androgen receptor (AR) transcript levels correlated with ACLY expression, and that inhibiting ACLY activity increased castration-resistant PCa (CRPC) cell sensitivity to AR antagonists via the ACLY/AMPK/AR axis. ACLY and AR inhibition reduced tumor cell proliferation and induced apoptosis (25). The reduced ACLY expression in PCa cells can increase caspase-3/7 intracellular levels, increase the proportion of early and late apoptotic cells, and inhibit PCa cell proliferation (26). ACLY inhibition can effectively enhance CRPC sensitivity to androgen deprivation therapy (ADT) and is expected to be a novel target for CRPC therapy.

ACC. The rate-limiting enzyme of FASN is ACC, which catalyzes the conversion of acetyl-CoA to malonyl-CoA. ACC has two isoforms: ACC1 (ACCα) and ACC2 (ACCβ) (27). The ACACA gene encodes ACC1, while the ACACB gene encodes ACC2. ACC1 and ACACA have been linked to the development and progression of numerous types of cancers, including breast (28), ovarian (29), liver (30) and colon cancer (31). The ACACA gene is upregulated in PCa tissues, and silencing the ACACA gene can inhibit PCa cell proliferation and induce apoptosis (32). The expression of the ACACA gene is associated with the local infiltration of tumor cells, lymph node metastasis and distant metastasis, and its expression level is positively associated with the Gleason score of PCa (33).

FASN. In the fatty acid *ab initio* synthesis pathway, FASN catalyzes the conversion of malonyl-CoA to 16-carbon fatty acid palmitate. In physiologically active human malignancies, FASN is frequently overexpressed, while it is barely detectable in healthy individuals. FASN controls tumor growth and body weight and is linked to PCa incidence and prostate cancer-specific mortality (34). Dysregulated lipid metabolism is a hallmark of PCa development and progression. FASN levels increase with the Gleason score of PCa tissue and can be used as a biomarker (35).

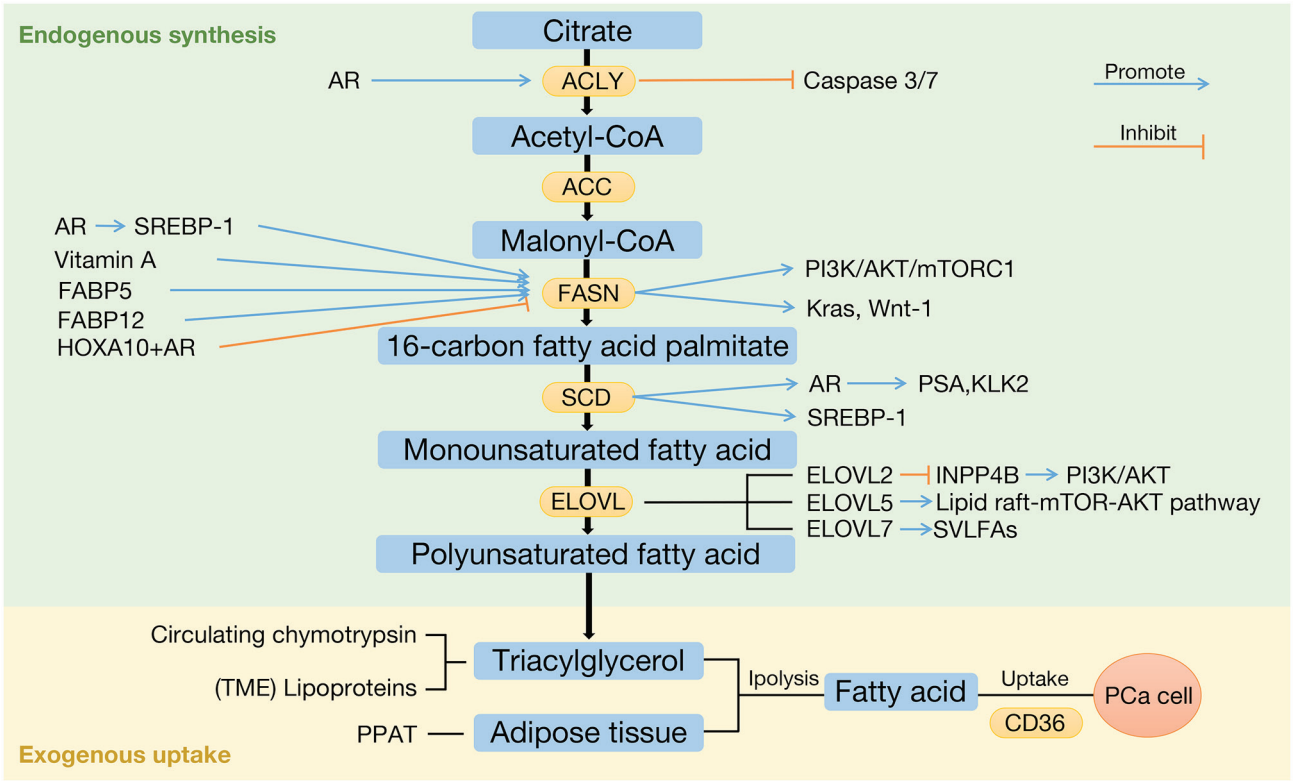

Figure 1. Exogenous uptake and endogenous synthesis of fatty acids. AR, androgen receptor; ACLY, ATP citrate lyase; ACC, acetyl-CoA carboxylase; FASN, fatty acid synthase; SCD, stearoyl-CoA desaturase; ELOVL, elongation of very-long-chain fatty acids protein; TME, tumor microenvironment; SREBP, sterol regulatory element binding protein; PCa, prostate cancer; PSA, prostate-specific antigen; SVLFAs, saturated very long chain fatty acids; KLK2, kallikrein-related peptidase 2.

FASN expression is regulated by the transcription factor, AR (36), and in the presence of AR, FASN can function as an oncogene for PCa, inhibiting apoptosis and exerting oncogenic effects (37). An enhanced FASN activity is closely linked to multiple oncogenic mechanisms, such as endoplasmic reticulum function and anti-genotoxic damage (38), the activation of the PI3K/AKT/mTORC1 pathway and the palmitoylation of oncogenes (e.g., Kras and Wnt-1) (39). FASN and AR-FL are found in 87% of human CRPC metastases. FASN/AR-V7 double-positive metastases have been found in 77% of patients treated with enzalutamide and/or abiraterone (40). Inhibiting FASN activity can result in cell cycle arrest and/or apoptosis, which can be used to inhibit PCa cell growth (38). Orlistat, a FASN inhibitor commonly used to treat obesity, has also been shown to have antitumor properties in breast cancer, *in situ* oral squamous cell carcinoma of the tongue and PCa (41-43).

SCD. SCD is a key enzyme for the synthesis of monounsaturated fatty acids. Human PCa has a higher ratio of monounsaturated to saturated fatty acids than normal prostate tissue, and SCD is highly expressed in PCa. SCD promotes the proliferation of AR-positive LNCaP cells, increases dihydrotestosterone (DHT)-induced AR transcriptional activity and increases prostate-specific antigen (PSA) and kallikrein-related peptidase 2 expression, and the inhibition of SCD attenuates the progression of PCa (44,45). A previous study discovered that inhibiting SCD activity with sterculic oil reduced LNCaP and PC3 cell viability, blocked the G2 cell cycle, decreased cell proliferation and promoted apoptosis (46). Furthermore, SCD1 is a transcriptional target of sterol regulatory element binding protein (SREBP)1 that mediates the ferroptosis-suppressing activity of SREBP1 by producing monounsaturated fatty acids, rendering PI3K/AKT/mTOR pathway-mutant PCa cells ferroptosis-resistant (47). SREBP1 is a central transcription factor regulating lipid metabolism, and SREBPs are discussed in more detail below.

ELOVL. Members of the ELOVL protein family are involved in the production of polyunsaturated fatty acids, which are critical components of cell membranes and are involved in the composition of the cytoskeleton, the regulation of cell membrane fluidity, signaling between the cell membrane and the cytoplasm, and the regulation of ferroptosis. ELOVL is also linked to ferroptosis regulation and plays a key role in tumorigenesis, development and drug resistance (48-50).

ELOVL7 is required for the synthesis of saturated very long-chain fatty acids and their derivatives, and its level is negatively associated with the survival of patients with PCa. ELOVL7 is promising as a novel molecular target for the treatment or prevention of PCa (51).

Compared to normal tissues, PCa tissues have higher levels of ELOVL2. A high expression of ELOVL2 indicates a better prognosis for patients with PCa, while ELOVL2 expression is adversely associated with the Gleason score. Low levels of ELOVL2 expression stimulate the growth of subcutaneous xenografts, colony formation, migration, invasion and PCa by downregulating inositol polyphosphate-4-phosphatase type II B to activate the PI3K/AKT signaling pathway. EVOVL2 may thus be a predictive biomarker and treatment target for PCa (52).

ELOVL5 is the main ELOVL expressed in primary and metastatic PCa, and the level of ELOVL5 in PCa is higher than that in non-malignant prostate tissue. When ELOVL5 is not present, mitochondrial function is disrupted, and oxidative stress is induced, inhibiting PCa cell proliferation and metastasis (15). When ELOVL5 is overexpressed, PCa cells exhibit an increased resistance to enzalutamide treatment, whereas ELOVL5 downregulation renderes PCa cells more responsive to enzalutamide treatment. The lipid raft/mTOR/AKT pathway is responsible for this effect, which has significant therapeutic implications for CRPC (53).

SREBPs. SREBP overexpression is associated with aggressive pathological features of human PCa (36). The set of genes activated by SREBP transcription factors is significantly upregulated in PML and PTEN double-null PCa (54). SREBPs are spliced into two biologically active products, SREBP-1 and SREBP-2 (55).

SREBP-1 is a master transcription factor that controls lipid metabolism. By binding to the FASN promoter region and either directly or indirectly activating FASN transcription, SREBP-1 can also participate in the transcriptional regulation of AR and fatty acid synthesis. This in turn can promote PCa growth, migration, invasion and depot resistance (36,56) and is positively associated with the clinical Gleason classification of human PCa (56). SREBP-1/FASN inhibition reduces fatty acid levels and lipid droplet accumulation in PCa cells (57). In healthy cells, there are two proteins SREBP-1, SREBP-1a and SREBP-1c, the latter of which is involved in controlling the *ab initio* production of endogenous fatty acids (55). SREBP-1 is transcriptionally regulated by microRNA-21 *in vitro* in cultured cells and mouse models (58) and can increase the production of reactive oxygen species, and NADPH oxidase 5 expression induces oxidative stress in PCa cells (56).

SREBP2 controls cholesterol production in healthy cells, and studies have shown that PTEN/p53-deficient cancers depend on cholesterol metabolism. Through the activation of SREBP2, PTEN/p53 deficiency transcriptionally elevates squalene epoxidase/monooxygenase (SQLE), and SQLE boosts cholesterol production and encourages tumor cell proliferation and survival (59).

In terms of medicine, the inhibition of SREBP is a possible novel strategy for the treatment of PCa. The SREBP pathway and AR signaling network can be targeted and blocked *in vitro* and *in vivo* by lipoinhibitors, new SREBP inhibitors, to decrease tumor development and distant metastasis with anti-prostate cancer action (36,54). In addition, drugs targeting the SREBP-2 pathway, such as tocotrienols, which can lower cholesterol levels, are also potential treatment options for PCa (60).

Fatty acid-binding proteins (FABPs) and peroxisome proliferator-activated receptor (PPAR). FABPs are multifunctional proteins that regulate fatty acid uptake, transport, signal transduction and intracellular lipid droplet formation (61) and regulate metabolic and inflammatory pathways that have been closely linked to obesity, metabolic diseases, cardiac dysfunction and cancer (62).

All five FABP genes, FABP4, FABP5, FABP12, FABP9 and FABP8, located on chromosome 8q21.13, are linked to PCa, and patients with high Gleason scores have higher levels of all five FABP mRNAs. Chromosome 8q21 is the most often amplified area in metastatic PCa (63,64).

FABP4 promotes the activation of PPARγ (65), and FABP5 promotes the activation of PPARγ and PPARβ/δ (66,67). Both PPARγ and PPARβ/δ are key regulators of lipid metabolism and energy homeostasis (68,69), and PPARγ is also a fatty acid-activated nuclear receptor and a driver of PCa metastasis (70). FABP4 can be secreted by adipocytes, is present in the circulation (71), and can promote the progression and metastasis of PCa (72). FABP4 is also an independent predictor of a high-grade Gleason score and prostate needle biopsy (PNB), and it is anticipated to be a novel biomarker for PNB optimization (73).

The promotion of PCa metastasis by FASN is largely dependent on the expression of vitamin A and FABP5 *in vivo* (74). By enhancing FA oxidation, the tricarboxylic acid cycle and oxidative phosphorylation, FABP5 deficiency may rewire metabolic pathways and increase ATP production by activating the PPAR signaling pathway (75). Vascular endothelial growth factor (VEGF) expression is controlled by androgens in androgen-dependent PCa cells; however, when PCa cells are no longer androgen-dependent, this route is replaced by the FABP5/PPAR/VEGF signaling pathway. Angiogenesis is another key element in the evolution of PCa (76). In the absence of FABP5, VEGF levels and microvessel density are reduced (77), PCa cells are less proliferative and invasive *in vitro*, and tumor growth and metastasis are decreased *in vivo* (78).

Through *ab initio* synthesis and improved fatty acid intake in the microenvironment, FABP12 upregulates FASN expression and promotes intracellular lipid buildup and PCa translocation (66). FABP12 also boosts the oxidative phosphorylation of fatty acid derivatives in the mitochondria, initiates epithelial-mesenchymal transition in PCa cells, and increases cell viability and invasiveness. FABP12-expressing cells treated with a carnitine palmitoyl transferase 1 (CPT1) inhibitor can prevent cell migration and mitochondrial β-oxidation mediated by FABP12 (79).

In terms of other FABPs, FABP1 and FABP2 levels are higher in PCa cells than in normal prostate cells, while FABP3 expression is lower (66).

Homeobox (HOX)A10. HOX genes are a group of highly conserved genes that control cell and tissue differentiation, morphogenesis, and homeostasis during development. A number of human tumors have an aberrant HOX gene expression (80,81). Different HOX genes are linked to the development of various prostate lobes, seminal vesicles and epididymis (80). HOXA10 is required for prostate development and can affect PCa progression by regulating fatty acid metabolism (82).

Human PCa frequently exhibits an abnormal HOXA10 expression, and HOXA10 levels are inversely associated with PCa cell differentiation, the Gleason score and clinical stage (83). It has been established that HOXA10 plays a crucial role in regulating AR signaling and adipogenesis. HOXA10 can bind AR to form a protein complex that inhibits AR from entering the FASN gene promoter, hence suppressing FASN gene transcription and preventing the progression of PCa to CRPC. By contrast, the downregulation of HOXA10 activates the FASN gene through AR signaling, promoting adipogenesis and the progression of PCa (82).

Fatty acid β-oxidation. Animals primarily catabolize fatty acids through β-oxidation. Fatty acid oxidation has been shown to be crucial in maintaining the malignant phenotype (84). In PCa cells, fatty acid β-oxidation is one of the main forms of energy supply (85,86), and the dysregulation of mitochondrial fatty acid β-oxidation promotes the pathogenesis of PCa (87). The mitochondria are the primary sites for fatty acid oxidation and sugar oxidative phosphorylation. PLC is required for fatty acid binding to cell surface receptors, and the PLC pathway increases intracellular calcium (Ca^{2+}) levels, which are involved in the dephosphorylation of Drp-1 protein, resulting in Drp-1 protein activation and mitochondrial division (88). The interaction between adipocytes and cancer cells is thought to mediate the regulation of mitochondrial dynamics via changes in intracellular Ca^{2+}, which affects fatty acid oxidation in mitochondria.

The fatty acid β-oxidation and fatty acid uptake capacity of cells are positively associated, whereas both are negatively associated with the process of fatty acid *ab initio* synthesis, indicating that fatty acid β-oxidation and fatty acid carbon chain lengthening are two processes that are mutually antagonistic (89). CPT1 is a key enzyme in fatty acid β-oxidation, and three CPT1 homologs have been identified, namely CPT1A, CPT1B and CPT1C (90). CPT1A can regulate the entry of fatty acids into mitochondria for β-oxidation (91), and the downregulation of CPT1A can attenuate the growth of PCa cells (92). In PCa samples, CPT1B, a crucial protein for rate limitation during mitochondrial β-oxidation, is increased and linked to prognostically unfavorable outcomes. Cell proliferation, S-phase distribution and invasive potential are all affected by CPT1B silencing. Conversely, CPT1B overexpression boosts AKT expression and phosphorylation, and markedly increases enzalutamide resistance in C4-2R cells (93). CPT1C is also involved in fatty acid catabolism and is a key gene for intracellular homeostasis (90).

3. Cholesterol and its ester metabolism in prostate cancer

Cholesterol uptake and synthesis

Exogenous uptake. The most prevalent steroid substance in the body is cholesterol, a steroidal lipid that makes up approximately one third of the plasma membrane's lipid content and is crucial for maintaining membrane fluidity and structural integrity (94). Additionally, cholesterol plays a key role in the metabolism of certain types of cancer and is a precursor to five key steroid hormones (glucocorticoid, mineralocorticoid, androgen, estrogen and vitamin D) (95).

Cholesterol in normal cells of the body is usually derived from two forms: Endogenous *in situ* synthesis and exogenous uptake (96). Only the liver and adipose tissue can normally generate cholesterol endogenously; all other tissues and organs primarily obtain cholesterol through external absorption. Low-density lipoprotein (LDL) and high-density lipoprotein (HDL) are involved in the exogenous uptake of cholesterol, which is primarily absorbed from food through the small intestine. LDL is transported into the cells by the LDL receptor (LDLr), and HDL is transported into the cells by scavenger receptor class B type 1 (SR-B1) (Fig. 2) (97,98). The key signaling pathways of human steroid-producing cells depend heavily on SR-B1, which has been linked to the entry and exit of cholesterol from cells (99).

Endogenous synthesis. The synthesis of cholesterol in the human body is very complex, and cells use acetyl-CoA as a raw material for *ab initio* synthesis, going through a total of ~30 steps, which can be broadly divided into four stages: The production of β-hydroxy-β-methylglutaryl-CoA, the production of mevalonate, the production of squalene and the production of cholesterol. Acetyl-CoA undergoes a series of stages consisting of β-hydroxy-β-methylglutaryl-CoA reductase, 2,3-oxidosqualene cyclase, squalene synthetase, SQLE, lanosterol synthase and farnesyl-diphosphate synthase-mediated enzymatic reactions (100,101), resulting in the synthesis of cholesterol (Fig. 2).

Cholesterol regulation and cholesterol ester accumulation. The key signaling pathways of human steroid-producing cells depend heavily on SR-B1, which has been linked to the entry and exit of cholesterol from cells (102). PCa cells can regulate intracellular cholesterol levels through various pathways, such as endocytosis, exocytosis, synthesis and degradation, and certain transcription factors play a critical role in this process. SREBP-2 promotes endogenous cholesterol synthesis and increases cholesterol levels (103); SR-B1 promotes cholesterol influx from lipoproteins in the body circulation into cells (104) and is necessary to drive cholesterol uptake required for steroidal and nonsteroidal biological pathways (102), while liver X receptor promotes cholesterol efflux (60) and downregulates AKT survival signaling in lipid rafts to induce the apoptosis of PCa cells (105).

To avoid the cytotoxicity of high cholesterol concentrations, the accumulation of cholesteryl esters (CEs) is common in high-grade PCa and metastases (16). Free cholesterol and fatty acids catalyzed by acyl coenzyme A-cholesterol acyltransferase (ACAT) can generate non-toxic CEs stored intracellularly (Fig. 2) (84,106,107), which serve as precursors for androgen synthesis and as raw materials for energy metabolism. In the absence of androgens, CEs are catalyzed by hormone-sensitive triglyceride lipase to produce free cholesterol (Fig. 2) (106,108), which in turn synthesizes androgens and promotes the proliferation of PCa cells (99). CE translocation out of the cell is mainly mediated by ATP-binding cassette subfamily A and ATP-binding cassette subfamily G member 1 proteins (109,110).

In addition to being closely related to PTEN deficiency and the activation of the PI3K/AKT/mTOR/SREBP signaling pathway, the accumulation of CEs in PCa cells may be caused by the anaerobic metabolism of tumor cells, which produces significant amounts of raw materials for cholesterol synthesis and the increased uptake of exogenous lipoproteins (16). The synthesis of CEs from free cholesterol and long-chain fatty acids is only catalyzed by the intracellular enzyme ACAT, and both of its major enzymes, ACAT1 and ACAT2, are controlled by androgens (108,111). This alteration in lipid metabolism is primarily caused by the activation of SREBP and LDLr, which boosts the esterification of ACAT and raises the uptake of foreign lipoproteins, increasing the accumulation of CEs in tumor cells. Reduced levels of specific essential amino acids and lipoproteins can prevent the buildup of CEs, which reduces tumor cell proliferation and invasiveness and attenuates tumor growth (16,107).

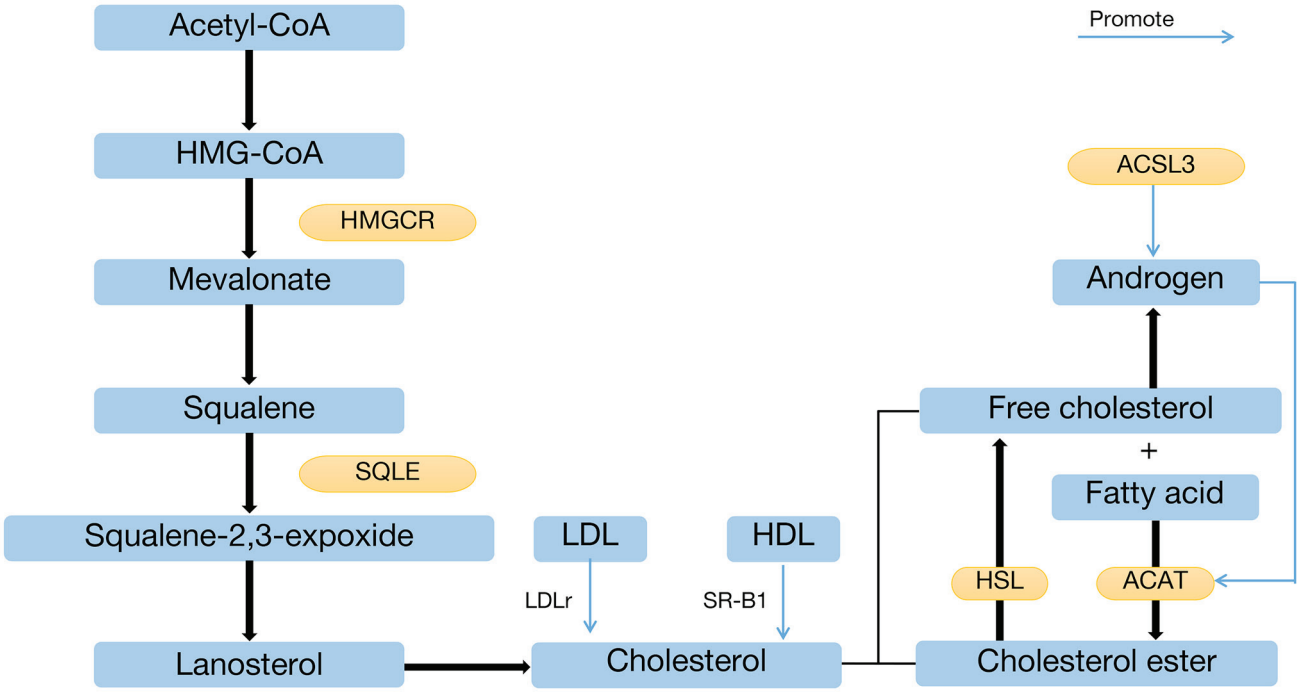

Figure 2. Metabolism of cholesterol and cholesterol esters. HMG-CoA, β-hydroxy-β-methylglutaryl-CoA; HMGCR, β-hydroxy-β-methylglutaryl-CoA reductase; SQLE, squalene epoxidase/monooxygenase; LDL, low-density lipoprotein; HDL, high-density lipoprotein; LDLr, low-density lipoprotein receptor; SR-B1, scavenger receptor class B type 1; HSL, hormone-sensitive triglyceride lipase; ACSL3, acyl-CoA synthetase long chain family member 3; ACAT, acyl coenzyme A-cholesterol acyltransferase.

Cholesterol metabolism and PCa progression. Cholesterol metabolism plays a critical role in cell membrane generation and cell proliferation, and it is linked to tumor cell survival and proliferation (112). As regards one of the primary elements of cell membranes, lipid rafts, cholesterol plays a role in the composition of these structures. Cholesterol also plays a role in cell signaling and has the ability to control particular proteins that are crucial for PCa cell growth and survival (113,114). Membrane cholesterol concentrations have a direct impact on the composition of signaling proteins and the transmission of signals. On the one hand, excessive cholesterol may cause abnormal signaling and alter the lipid-protein balance. On the other hand, lower cholesterol levels alter lipid raft integrity and prevent oncogenic signaling complexes from functioning (114).

Lipid rafts have numerous functions and are involved in the translocation and sorting of intracellular molecules, the down-regulation and recycling of receptors, and the targeted export of proteins and lipids. Lipid rafts are also signaling platforms that are associated with a large number of signaling proteins (115), including epithelial growth factor receptor (116), other tyrosine kinase receptors (117), estrogen receptor (118), AR (119) and fatty acid synthase receptor (120). The function of AKT is controlled by the amount of cholesterol in the membrane, and the AKT subpopulation within lipid rafts has different substrate specificity from non-lipid raft AKT, is involved in cell growth and survival, and controls crucial genes related to lipid and cholesterol synthesis at the transcriptional level (121). Increased cholesterol inhibits apoptosis in cells by working with lipid rafts. Additionally, since cholesterol synthesis and the cell cycle are tightly connected, reducing cholesterol levels with blockers may result in the inhibition of cell growth, which in turn causes PCa cells to undergo apoptosis (122).

Androgens are steroidal compounds, cholesterol is an essential androgen synthesis precursor (95), and PCa cells can use cholesterol and adrenal androgens to produce testosterone and DHT. Intracellular cholesterol promotes PCa progression as a substrate for *de novo* androgen synthesis and through the regulation of AKT signaling (123). By controlling steroidogenic genes, the acyl-CoA synthetase long-chain family member 3 (ACSL3) participates in the synthesis of fatty acyl-CoA ester, limits the catabolism of active androgens and stimulates steroid biosynthesis in tumors, all of which contribute to the progression of PCa. Since ACSL3 is substantially more highly expressed in CRPC than in hormone-sensitive PCa, ACSL3 may be a viable target for CRPC therapy (124).

Blood cholesterol levels are also associated with the progression of PCa, and it has been shown that hypercholesterolemia caused by high cholesterol and high-fat diets increases the risk of developing PCa in older males (125-127) and may also promote the growth and metastasis of PCa (128), whereas low blood cholesterol levels slow the growth of PCa (123,129), and the risk of high-grade PCa is lower in patients with lower blood cholesterol levels than in those with high blood cholesterol levels (130). Statins have been shown to be effective in reducing the risk of PCa (123,125,131,132).

However, circulating blood cholesterol levels in tumor patients are decreasing (133), a phenomenon that may be due to the Warburg effect caused by abnormal energy metabolism in malignant tumor cells (134), which have an enhanced metabolic rate and require large amounts of cholesterol to maintain rapid tumor growth. Therefore, although some studies have suggested that lower circulating blood cholesterol levels may be associated with an increased risk of developing PCa (135), a reasonable explanation may be that hypocholesterolemia is not

a risk factor for tumor development, but rather a result of metabolic reprogramming caused by the development of tumors.

4. Phospholipid metabolism in prostate cancer

The phospholipids in the plasma membrane mainly include phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylinositol (PI), phosphatidylserine (PS) and sphingomyelin (SM). Current research on phospholipids associated with PCa is focused on diagnostic and prognostic aspects.

There is a significant difference between PE and glycerophosphatidylethanolamine (and their ratios) between PCa and benign prostatic hyperplasia (136), and *in vitro* ^{31}P nuclear magnetic resonance can be used to detect phospholipid metabolites to assist in the diagnosis of PCa (137). Moreover, phospholipids can be radiolabeled and developed as PET imaging agents for PCa (138). Gradients of changes in the intensity of various lipids, such as PC, PS, PI, phosphatidic acid and cardiolipin, are associated with increases in Gleason scores (139). In CRPC, high levels of sphingolipids are associated with a poor prognosis, and PC, SM and ceramide are associated with a shorter survival (140).

Annexin (ANX) is a family of intracellular proteins that binds membrane phospholipids using calcium ions and is important in the diagnosis and prognostic monitoring of PCa. ANX1 expression is reduced in PCa and high-grade prostatic intraepithelial neoplasia (PIN) and is associated with a lower Gleason score (141). ANX2 expression decreases with the progression of PCa and is significantly and negatively associated with the Gleason score (142). Both benign prostatic epithelium and high-grade PIN samples contain ANXA3; however, the staining intensity is lower in PIN lesions than it is in benign prostatic epithelium. In addition, ANXA3 is negatively associated with the Gleason score and is a stand-alone poor prognostic marker in PCa (143). ANXA7 is a suppressor of tumorigenesis and metastasis in PCa, and activated ANXA7 GTPase promotes apoptosis in PCa cells (144). Statins inhibit the proliferation, migration and invasion of androgen-dependent PCa cells by upregulating ANXA10 (145). The combined detection of ANX and serum PSA levels may help to improve the accuracy of the early diagnosis of PCa.

Phospholipids have been linked to PCa treatment in addition to functioning as biomarkers. PS is normally anchored to the inner side of the cell membrane; however, when complex conditions, such as phospholipid translocator protease inactivation in tumor cells occur, PS is translocated to the outer side of the cell membrane (146). In response to this feature of PS, a number of molecules targeting tumor PS have been developed to provide new insight into for tumor therapy. Mitochondrial 2,4-dienoyl-CoA reductase 1 (DECR1) can participate in the dynamic balance of redox by controlling the balance between saturated and unsaturated phospholipids. The knockdown of DECR1 induces endoplasmic reticulum stress and increases the sensitivity of CRPC cells to ferroptosis, and DECR1 deficiency *in vivo* impairs lipid metabolism and inhibits CRPC tumor growth (147). It has been reported that DECR1 and medication resistance in CRPC are closely connected. To shield siRNA from enzymatic degradation and to increase siRNA release with gene silencing and anticancer effects for the treatment of CRPC, amphiphilic phospholipid peptide dendrimers can facilitate the efficient delivery of siRNA targeting heat shock protein 27 (148).

5. Lipid metabolism and the diagnosis and treatment of prostate cancer

The mechanism by which PCa develops into malignant cancer is significantly influenced by abnormalities in lipid metabolism. It is anticipated that several of the aforementioned proteins that are involved in the control of lipid metabolism will serve as novel targets for the detection and treatment of PCa. These implications are summarized and presented in Table I.

Additionally, there is a strong association between lipid concentrations and PCa. Lipoprotein A [Lp(a)] is a lipid biomarker, and Lp(a) concentrations are associated with an increased risk of developing PCa; lowering Lp(a) levels may prevent the development of PCa (149). An elevated Gleason score and likelihood of lymph node metastases are both associated with elevated cholesterol levels (150). A higher likelihood of PCa recurrence is also linked to elevated levels of triglycerides and cholesterol (151). Extracellular vesicles from PCa have been identified to mediate intercellular communication with bone marrow cells in a cholesterol-dependent manner, promoting PCa cell metastasis (152).

Statins are currently the primary treatment agents for aberrant lipid metabolism; however, it is uncertain whether the use of statins increases the risk of developing PCa (153). Some studies (154-157) have demonstrated that there is no association between statin use and the risk of developing PCa, while other studies (158-160) have indicated that statin use reduces the risk of developing advanced PCa and the risk of fatal PCa. Statin use has been reported to attenuate the increased aggressiveness of PCa caused by a high intake of saturated fats (161); combining statins has been shown to improve PCa sensitivity to specific chemotherapeutic drugs (162), and the use of statins following ADT initiation has been found to improve the prognosis of patients with PCa (163). From another perspective, traditional PCa treatment drugs also significantly affect lipid metabolism. Butler *et al* (164) discovered that the treatment of primary tumor 'explants' with the AR antagonist, enzalutamide, caused significant changes in lipid subsets within only 48 h. The targeted inhibition of tumor-associated lipid profiles caused significantly decreased cell proliferation and induced apoptosis in tissue explants (164).

6. Conclusions and future perspectives

Lipid metabolism is closely related to the development and progression of PCa and has become a hot research topic in recent years. The metabolism of fatty acids, cholesterol and phospholipids, particularly key genes and proteins in various lipid metabolism pathways, play a crucial role in the growth, invasion, migration and malignant transformation of PCa and may potentially be good diagnostic and prognostic markers or even potential therapeutic targets (Table I).

Abnormalities in lipid metabolism appear to be associated with the malignant transformation and poor prognosis of PCa. It may be possible to target abnormal

Table I. Proteins with altered levels in prostate cancer.

Protein	Alteration	Function	Clinical association	(Refs.)
CD36	Increased	Promotes growth	Therapeutic target	(22)
ACLY	Increased	Promotes growth	Therapeutic target	(24-26)
ACC	Increased	Promotes growth and metastasis	Prognostic marker, therapeutic target	(32,33)
FAS	Increased	Promotes growth and metastasis	Prognostic marker, therapeutic target	(34-42)
SCD	Increased	Promotes growth	Therapeutic target	(44-47)
ELOVL7	Increased	Promotes growth	Prognostic marker, therapeutic target	(51)
ELOVL2	Increased	Inhibits growth and invasion	Prognostic marker, therapeutic target	(52)
ELOVL5	Increased	Promotes growth and metastasis	Therapeutic target	(15,53)
SREBP-1	Increased	Promotes growth and metastasis	Prognostic marker, therapeutic target	(36,56-58)
SREBP-2	Increased	Promotes growth and metastasis	Prognostic marker, therapeutic target	(59)
FABP4	Increased	Promotes growth and metastasis	Prognostic/predictive/ diagnostic marker	(72,73)
FABP5	Increased	Promotes growth and metastasis	Prognostic marker	(74-78)
FABP12	Increased	Promotes growth and metastasis	Prognostic marker	(66)
FABP3	Decreased	N/A	N/A	(66)
HOXA10	Decreased	N/A	Prognostic marker	(82,83)
CPT1	Increased	Promotes growth and invasion	Prognostic marker, therapeutic target	(90-93,165)
SR-B1	Increased	Promotes growth and metastasis	Prognostic marker, therapeutic target	(98,99,102,104)
LXR	Decreased	Promoted cell apoptosis	N/A	(60,105)
ACAT	Increased	N/A	Prognostic/diagnostic marker	(84,106,107)
HSL	Increased	Promotes growth	N/A	(99,106,108)
ACSL3	Increased	Promotes growth	Therapeutic target	(124)
PC	Increased	N/A	Prognostic marker	(139)
PI	Increased	N/A	Prognostic marker	(139)
PS	Increased	N/A	Prognostic marker, therapeutic target	(139)
SM	Increased	N/A	Prognostic marker	(140)
ANX	Decreased	N/A	Prognostic/diagnostic marker, therapeutic target	(141-145)
DECR1	Increased	Promotes growth	Prognostic marker	(147)

ACLY, ATP citrate lyase; ACC, acetyl-CoA carboxylase; SCD, stearoyl-CoA desaturase; ELOVL, elongation of very-long-chain fatty acids protein; SREBP, sterol regulatory element binding protein; FABP, fatty acid-binding protein; HOX, homeobox; CPT1, carnitine palmitoyl transferase 1; SR-B1, scavenger receptor class B type 1; LXR, liver X receptor; ACAT, acyl coenzyme A-cholesterol acyltransferase; HSL, hormone-sensitive triglyceride lipase; ACSL3, acyl-CoA synthetase long chain family member 3; PC, phosphatidylcholine; PI, phosphatidylinositol; PS, phosphatidylserine; SM, sphingomyelin; ANX, annexin; DECR1, 2,4-dienoyl-CoA reductase 1; N/A, not applicable.

lipid metabolic pathways to modify this vulnerability. For example, in the setting of increased obesity, PCa is more likely to progress to advanced-stage or more aggressive PCa, and it may be possible to PCa or reduce the risk of developing more malignant PCa by avoiding obesity and the use of statins. PPAT provides high levels of fatty

acids to alter the TME and promote PCa progression, and altering the TME through interactions between lipids and immune cells may be an option. Although it may currently not be practical to replace conventional PCa therapy with medications that target lipid metabolic pathways, perhaps the use of lipid-targeted medications in combination with other medications could increase the treatment efficacy and prognosis of patients with PCa. At this time, it is unlikely that lipid biomarkers will completely replace classical PCa markers; however, they are more likely to be a component of a combined diagnostic strategy that will help with diagnosis and prognosis. However, further prospective studies are required for validation.

Currently however, identifying strategies to accurately assess the efficacy and biosafety of these drugs, to mitigate the toxic side-effects of the combination of related drugs and to determine the variability of lipid biomarkers in different populations, as well as the elucidation of the mechanisms of action of these key regulatory molecules are all urgent scientific challenges that need to be addressed. It is considered that these issues may soon be resolved, bringing new advances to the diagnosis and treatment of PCa.

Acknowledgements

Not applicable.

Funding

The present study was supported by grants from the National Natural Science Foundation of China Youth Science Foundation Project (no. 81802571), and the Zhejiang Medical and Health Science and Technology Project (no. 2019RC039).

Availability of data and materials

Not applicable.

Authors' contributions

ZZ and WW wrote and completed the manuscript and abstract. PK and KF consulted the relevant literature and completed the English revisions. CL TS, YS and XD completed the design of the framework of the manuscript, and completed the figures and tables. WL and ZT provided constructive feedback and guidance. WL completed critical revisions and proofread the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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