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Review Article

The dysfunctional lipids in prostate cancer

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Abstract: Prostate cancer (PCa) is well-recognized as a lipid-enriched tumor. Lipids represent a diverse array of molecules essential to the cellular structure, defense, energy, and communication. Lipid metabolism can often become dysregulated during tumor development. The increasing body of knowledge on the biological actions of steroid hormone-androgens in PCa has led to the development of several targeted therapies that still represent the standard of care for cancer patients to this day. Sequencing technologies for functional analyses of androgen receptors (ARs) have revealed that AR is also a master regulator of cellular energy metabolism such as fatty acid ß-oxidation, and de novo lipid synthesis. In addition, bioactive lipids are also used as physiological signaling molecules, which have been shown to be involved in PCa progression. This review discusses the potent player(s) in altered lipid metabolism of PCa and describes how lipids and their interactions with proteins can be used for therapeutic advantage. We also discuss the possibility that the altered bioactive lipid mediators affect intracellular signaling pathway and the related transcriptional regulation be of therapeutic interest.

Keywords: Lipid metabolism, bioactive lipids, prostate cancer, cancer progression

Introduction

A key player in prostate cancer (PCa) development and progression is the androgen receptor (AR). Pathologically, PCa is known as a lipid-rich tumor [1]. Indeed, several genes encoding lipogenic enzymes can be regulated by androgen [2-7]; increased synthesis of fatty acids and cholesterol is governed by androgens through stimulation of the expression of whole sets of lipogenic enzymes, covering the entire pathways of fatty acid (FA) pathway. The resulting increase in lipogenesis helps synthesise the synthesis of key membrane components (phospholipids, cholesterol) and is a major hallmark of cancer cells. In addition, an increase in total cholesterol and in triglycerides duration of androgen deprivation therapy (ADT) that ranges from 24 weeks to 12 months [8-12]. While increased lipogenesis is initially androgen-responsive it persists or re-emerges with the development of castration resistant PCa (CRPC), indicating that lipid metabolism is a fundamental aspect of PCa cell biology. In this review, we discuss the lipid landscape and the possible underlying mechanisms mediating PCa development and progression.

Lipogenesis in prostate carcinogenesis

Cancer cells usually exhibit the ability of rapid proliferation. In order to deal with this altered growth rate, changes in the cellular metabolic pathways are always displayed [13, 14]. Since 1950s, researchers have noticed the metabolic dysregulation in cancer cells and it has been widely studied. Some of the most well-known alterations include Warburg effect [15] and increased glutamine metabolism [16]. Recently, lipid metabolism emerges as a more and more important role in cancer. Since lipids supply energy, provide signaling molecules and synthesize the cellular membrane [16-18], highly proliferative cancer cells often have a higher demand for lipids and exhibit an abnormally active lipogenesis [19]. Unlike most normal somatic cells, which mainly utilize the exogenous lipids, studies have shown that many cancer cells mainly use de novo FA synthesis to increase total FA [8], regardless of abundant extracellular lipid content [20-22]. Fatty acid synthase (FASN) is the key enzyme in fatty acid synthesis. Since the identification of onco-antigen OA-519 as a FASN in breast cancer 20 years ago, it has now become a well-estab-

lished oncogene in numerous types of cancer, including prostate, ovary, colon, endometrium, lung, bladder, stomach, esophagus and pancreas [23, 24]. Higher FASN expression is associated with poor survival and disease recurrence in PCa patients [25-27]. Even in some pre-invasive lesions, elevated FASN can be detected [27]. Consistent with the clinical observation, immortalized prostate epithelial cells with overexpressing FASN exhibit increased invasion ability [28]. In addition, ATP citrate lyase (ACLY) is the first enzyme of the reaction chain and serves as an important bridge between glycolysis and lipogenesis by catalyzing coenzyme A (CoA) and citrate that is a product of glycolysis [29, 30]. Clinically, increased ACLY represents an unfavorable biomarker for PCa and several other cancer types including bladder, renal, non-small cell lung, colorectal, breast, liver and gastric cancers [31, 32].

Although lipogenesis is considered to be the major source of FA in cancer cell, it is reported that some cancers may also adopt lipolysis as an additional method to acquire FA [33]. During certain metabolic stresses, cancer cells may switch from de novo FA synthesis to scavenging extracellular lipids [34]. Lipoprotein lipase (LPL) is the key enzyme for extracellular lipolysis, which hydrolyzes the triglycerides (TGs) in chylomicrons or very low-density lipoproteins (VLDL), and the FA produced from hydrolysis are then taken up by the cancer cells through the transmembrane channel CD36 [35, 36]. Indeed, both LPL and CD36 are ubiquitously expressed in PCa tissues [33, 36], suggesting lipolysis may also contribute to PCa development.

Bioactive lipid mediators in PCa progression

Phosphoinositides (PIs) are major second messengers, which transmit signals from activated growth factor receptors on the cellular surface to the interior of the cells. Saturated and unsaturated fatty acids combine with glycerol-3-phosphate in glycerolipid biosynthesis which is highly dependent on glycerol-3-phosphate acyltransferase (GPAT) to produce PIs and phosphoglycerides [37]. One of the most prominent lipids of this class is phosphatidylinositol (3,4,5)-trisphosphate [PtdIns (3,4,5) P3; PIP3], which is produced by PI3K in response to growth factor signaling and mediates the recruitment and activation of Akt [38]. In contrast, PTEN (phosphatase and tensin homolog deleted on chromosome ten) is a PIP3 phosphatase and commonly downregulated in PCa [39]. Other lipid second messengers, such as lysophosphatidic acid (LPA), phosphatidic acid (PA) and diacylglycerol (DAG), which are produced by the different phospholipases [40]. LPA can be produced by the extracellular lysophospholipase or autotaxin, which can activate cell proliferation, migration and survival via binding to G-protein-coupled receptors [41]. PA can bind to the mTOR polybasic domain, which is essential for its activation. The phosphoinositide-specific phospholipases C (PLC) can transform phosphatidylinositol 4,5-bisphosphate [PtdIns (4,5) P2] into the DAG and inositol 1,4,5-trisphosphate. Several studies demonstrated that PLCγ1 plays an important role in PCa metastasis [42, 43].

Ceramide as the central molecule in the sphingolipid metabolism. The balance between the levels of sphingosine-1-phosphate (S1P) and its metabolic precursors ceramide and sphingosine has been regarded as a rheostat that could determine cell fate [44, 45]. For example, ceramide mediates numerous cell-stress responses such as induction of apoptosis and cell senescence, whereas S1P plays a pivotal role in cell survival, migration, and inflammation. Ceramide production was correlated with enhanced apoptosis in LNCaP cells treated with TNF-α and irradiation. Ceramide treatment can specifically kill PCa cells but not normal prostate epithelial cells by decreasing c-myc expression [46].

Accumulating evidence links S1P produced by Sphingosine kinase 1 (Sphk1) with PCa; Sphk1 is elevated in primary PCa lesion compared to adjacent benign tissue [47, 48]. Using PCa cell culture models, elevated Sphk1 can promote PCa invasion, which is mediated by Sphungosine-1-phosphate receptor 4 (S1PR4)-Matriptase activation [49]. Also, upregulation of the SphK1-S1P pathway is associated with chemoresistance in PCa cells [50]. A selective SphK1 inhibitor (such as FTY720) can trigger apoptosis of a variety of PCa cells including androgen-responsive LNCaP, androgen variant-expressing 22RV1 and castration resistant PC3 cell [51-53]. Furthermore, hypoxia can activate Sphk1 enzyme activity leading to the stabilization of HIF-1α levels, which could lead to radio-

resistant PCa [54]. These results indicate the critical role of Sphk1 in PCa survival.

Regulators of lipid metabolism in PCa

Sterol regulatory element-binding proteins (SREBPs) are transcription factors that can mediate the homeostasis of cholesterol and fatty acids [55]. SREBP-1 mainly regulates genes in FA synthesis and is highly elevated in PCa [56]. SREBP-2 is responsible for cholesterol synthesis. Upregulated of SREBP-2 has been found in PCa patient tumor tissues [57]. Several lines of evidence indicate that androgens activate the SREBP pathway (1) Androgens stimulate the nuclear accumulation of mature SREBP [2]. (2) Androgen stimulation of key lipogenic genes (fatty acid synthase, HMG-CoA synthase) is abolished when the SREBP binding sites in the proximal promoter are deleted or mutated [2-5]. (3) Introduction of a dominant-negative SREBP strongly suppresses the lipogenic effects of androgens [2-5]. In several instances, the lipogenic effects of androgens are more pronounced than estimated from the changes in mRNA levels of lipogenic genes, suggesting that also translational and/or post-translational mechanisms are involved [3]. Moreover, PI3K/Akt/mTOR can upregulate the SREBPs expression and stabilize the nuclear form of SREBP-1 nuclear form, and then promote its target gene expression via decrease in the expression of Fwb-7 in mediating fatty acid synthesis and cholesterol uptake. SREBPs can be activated by SREBP-cleavage-activating protein (SCAP) to drive expression of enzymes needed for lipid syntheses, such as fatty acid synthase (FAS), 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG CoA-R) and low-density lipoprotein receptor (LDLR) [58]. SREBP-1 can upregulate the expression of ATP citrate lyase (ACL), acetyl-CoA carboxylase (ACC) and FAS to promote fatty acid synthesis and enhance cholesterol uptake via upregulation of LDLR, thereby promoting the cancer tumor growth [59, 60]. Plk1 can induce activation of the PI3K/AKT/mTOR/GSK3β and AR pathways and increase of lipid biosynthesis [58]. Fatostatin suppresses Plk1/SREBP, which leads to the inhibition of cell proliferation, invasion, and migration, and to arrest cancer cells at the G2/M checkpoint in both of androgen-responsive LNCaP and androgen-insensitive C4-2B PCa cells [61]. The PI3K/Akt/mTOR/SREBP signaling pathway has a positive feedback regulatory loop, which can boost Akt expression in cell migration, tumor growth, and metastasis [62].

Peroxisome proliferator-activated receptor gamma (PPARγ) is, a ligand-dependent transcription factor belonging to the nuclear hormone receptor superfamily, considered a master regulator for the genes involved in FA synthesis and lipogenesis. PPARγ protein level is found significantly elevated in advanced PCa when compared to localized PCa or benign prostatic hyperplasia [63, 64]. Higher protein expression of PPARγ is also associated with shorter patient survival duration [65]. In prostate-specific *Pten-/-* mouse model, over-expression of the PPARγ protein is associated with significantly decreased survival and increased metastases to the lungs and lymph nodes compared to littermate controls [66]. The PPARγ inhibitor (antagonist GW9662) also decreases the growth of human PCa cells in culture [66]. Furthermore, there is a reciprocal regulation between PPARγ and androgen receptor (AR) activity; DHT treatment decreased PPARγ mRNA and protein levels in LNCaP C4-2 and VCaP cell lines [67]. Noticeably, PPARγ plays a key role in IL-6-elicited neuroendocrine differentiation of PCa (NEPC) [68]. Altogether, these data support the development of PPARγ inhibition as a new strategy of PCa treatment.

The family of PPARγ coactivator 1-alpha coactivators (PGC1) have two isoforms, PGC1 α and β, that are transcriptional coactivators and can regulate the mitochondrial biogenesis and functions including FA and lipid metabolism. PGC1α plays a major role in the rapid metabolically active tissues such as liver, cardiac, skeletal muscle, kidneys, and adipose tissue [69, 70] in energy-demanding situations. The PGC1α protein is associated with PPARγ (the role in adipogenesis, thermogenesis, and mitobiogenesis), nuclear respiratory factor 1-2 (Nrf1-2), Forkhead box O3 (FoxO3a), cyclic-AMP (cAMP) response element-binding protein (CREB) and estrogen-related receptor-α (ERRα) [69-71]. Androgens signaling can increase the expression of PGC1α in PCa cells [72]. Clinically, in PCa patient specimens, a significant correlation between PGC1α with tumor proliferation was reported [72].

Mammalian silent information regulator 1 (SIRT1) is a nicotinamide adenine dinucleotide

(NAD)-dependent histone deacetylase, which plays a major role in multiple physiological processes such as stress responses, metabolism, apoptosis, and calorie restriction, etc [73-77]. SIRT1 has been demonstrated to be an oncogene in mouse PCa model with PTEN deficiency [78]. Several studies indicated that SIRT1 was associated with the class III deacetylases and its targets, such as p53, PPARγ, PGC1α, Beclin 1 and β-catenin [79-82]. SIRT1 overexpression induces epithelial-to-mesenchymal transition (EMT) in epithelial prostate cells and increases PCa cell migration in vitro and metastasis in vivo. In contrast, inhibiting the expression of SIRT1 in PCa cells restores cell-cell adhesion and reverses EMT. Thus, SIRT1 can regulate the expression of the E-cadherin epithelial markers and γ-catenin, and the mesenchymal markers fibronectin and N-cadherin [83].

AMP-activated protein kinase (AMPK) is a serine/threonine protein kinase consisting of a catalytic subunit (α) and two regulatory subunits (β and γ) [84, 85]. Once the activation of AMPK redirects lipid metabolism towards increased catabolic fatty acid oxidation and decreased anabolic lipid synthesis via the phosphorylation of acetyl-CoA carboxylases (ACCs) phosphorylation. ACCs represents the first step in de novo lipid synthesis, which responsible for the carboxylation of acetyl-CoA to form malonyl-CoA [86]. Several studies showed that knockout of one of the catalytic subunits of AMPK, which support a tumor suppressive role for AMPK in PCa [87-89]. Elevation of both activated AMPK (Threonine 172 phosphorylation) and acetyl-CoA carboxylase (Serine 80 phosphorylation) were detected in PCa clinical samples compared to surrounding benign tissues. AMPK was also associated with the progression of PCa with higher Gleason grades and advanced stages [72, 88, 89]. Collectively, these studies support the clinical relevance of AMPK in PCa development.

Conclusion

Increased lipogenesis is an important hallmark in PCa development and androgen plays a critical role to stimulate lipogenesis. The resulting increase in the coordinate expression of multiple regulators or enzymes involved in the gene transcription, metabolism and transport of FAs and cholesterol mainly results in the synthesis of phospholipids partitioning in various malignant activities. While increased lipogenesis is initially androgen-responsive it persists or re-emerges with the development of CRPC or NEPC, indicating that lipogenesis is a fundamental aspect of PCa cell biology and is a potential target for anti-neoplastic therapy in advanced PCa.

Disclosure of conflict of interest

None.

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