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Metabolomic profiling for the identification of novel diagnostic markers in prostate cancer: an update

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Abstract

Introduction: An altered metabolic regulation is involved in the development and progression of different cancer types. As well as this, many genes associated with tumors are shown to have an important role in control of the metabolism. The incidence of prostate cancer (PCa) is increased in men with metabolic disorders. In particular, obesity is an established risk factor for PCa. An increased body mass index correlates with aggressive disease, and a higher risk of biochemical recurrence and prostate cancer-specific mortality. Increased lipogenesis is also one of the most significant events in PCa metabolism reprogramming.

Areas covered: In this article, we provide an updated review of the current understanding of the PCa metabolome and evaluate the possibility of unveiling novel therapeutic targets.

Expert opinion: Obesity is an established risk factor for PCa, and an increased BMI correlates with aggressive disease, and a higher risk of biochemical recurrence and prostate cancer-specific mortality. PCa metabolome is characterized by the accumulation of metabolic intermediates and an increased expression of genes in the tricarboxylic acid cycle, the induction of de novo lipogenesis and cholesterogenesis. PCa cells can induce different alterations in their microenvironment by modulating the crosstalk between cancer and stromal cells.

Keywords: metabolomics, prostate cancer, lipid metabolism, fatty acids, cholesterol, SREBP

Article Highlights

- Prostate cancer (PCa) is the most common male tumor and the second leading cause of cancer death in men worldwide. Recent estimates have calculated that in 2019, 174,650 new cases will be diagnosed and 31,620 patients will die of PCa in the United States
- Obesity is an established risk factor for PCa, and an increased body mass index (BMI) correlates with aggressive disease, and a higher risk of biochemical recurrence and prostate cancer-specific mortality. In addition, increased BMI values are associated with disease upstaging and upgrading in low-risk PCa patients who are candidates for active surveillance.
- PCa is characterized by two distinctive metabolic fingerprints, reflecting their molecular phenotype: phospho-AKT^{high}/MYC^{low} versus phospho-AKT^{low}/MYC^{high} tumors
- PCa metabolome is characterized by the accumulation of metabolic intermediates and an increased expression of genes in the tricarboxylic acid cycle. These findings are in accordance with the reactivation of mitochondrial aconitase, the restoration of metabolic flux through the Krebs cycle, and the induction of de novo lipogenesis and cholesterogenesis.

- PCa cells are able to induce different alterations in their microenvironment by modulating the crosstalk between cancer and stromal cells.

1. Introduction

Prostate cancer (PCa) is the most common male tumor and the second leading cause of cancer death in men worldwide. Recent estimates have calculated that in 2019, 174,650 new cases will be diagnosed and 31,620 patients will die of PCa in the United States [1].

Despite the introduction of PSA as PCa biomarker, up to 30% of patients with clinically localized disease will undergo disease recurrence and metastatic dissemination after therapy with curative intent [2,3]. Androgen-deprivation therapy (ADT) has been the standard of care for these patients with advanced disease. The majority of patients will respond to ADT, but most of them will then become refractory within a few months. Targeting the androgen receptor (AR) pathway continues to have an important role in the treatment of PCa, even in the castration-resistant phase of the disease. Recent studies have shown that multiple mechanisms are involved in PCa resistance to ADT. These include genetic alterations in the AR gene, (such as point mutations and gene amplification), AR splice variants, ligand-independent activation of AR, activation of alternative signaling pathways that by-pass AR, and intratumoral and alternative androgens production [4-6]. In this scenario, it is important to explore alternative regulatory pathways involved in cancer-specific features such as autophagy and cell metabolism [7,8]. Many studies have demonstrated that an altered metabolic regulation is involved in the development and progression of different cancer types [9], as well as that many genes

associated with these tumors are shown to have an important role in control of the metabolism [10-14].

The incidence of PCa, like many other tumors including renal cell carcinoma and bladder cancer, is increased in men with metabolic disorders [15-23]. In particular, obesity is an established risk factor for PCa, and an increased body mass index (BMI) correlates with aggressive disease, and a higher risk of biochemical recurrence and prostate cancer-specific mortality [24-26]. In addition, increased BMI values are associated with disease upstaging and upgrading in low-risk PCa patients who are candidates for active surveillance [27].

In a previous article [28], we reviewed the role of novel molecular markers, based on an in-depth analysis of the available data on the PCa metabolome. In this new article, we provide an updated review of the current understanding of the PCa metabolome and evaluate the possibility of unveiling novel therapeutic targets.

2. Evidence of two distinctive metabolic profiles in prostate cancer

Phosphatase and tensin homolog tumor suppressor on chromosome 10 (PTEN) genomic loss is the most frequent genetic alteration observed in human prostate cancer [29]. PTEN functions as a direct antagonist of the activity of class I PI3K, a family of enzymes that phosphorylate phosphatidylinositol-4, 5-bisphosphate (PIP2) to generate phosphatidylinositol-3,4, 5-trisphosphate (PIP3). PIP3 is critical in mediating the activation of a number of important downstream effector molecules, including Ser/Thr protein kinase AKT/PKB, which further activates the mammalian target of rapamycin (mTOR) [30]. It has also been shown that gain of MYC and loss of PTEN in combination were the only changes associated with an elevated risk of PCa–specific mortality, raising the hypothesis

that MYC gain and PTEN loss may cooperate to drive genomic instability and lethal disease [31].

AKT/PKB activation supports cell survival, suppresses apoptosis, promotes anabolic metabolism, and drives the Warburg effect [32]. MYC, a transcriptional regulator, has also been found to directly regulate aerobic glycolysis, but in addition it promotes glutaminolysis and regulates lipid metabolism [33,34]. Although both AKT and MYC have overlapping effects in controlling glucose metabolism, they can activate different cellular metabolic programs according to their differential expression [35]. In this scenario, Priolo et al. demonstrated that prostate cancer cells undergo a distinctive reprogramming of their metabolism in accordance with the differential expression and activation of these two oncoproteins [36]. In particular, whereas AKT signaling activation was associated with an enhanced aerobic glycolysis (Warburg effect), pentose phosphate pathway, and fructose metabolism, high MYC expression induced a dysregulated lipid metabolism, associated with an increased expression of glutaminase and reduced expression of some glycolytic components. So, these results identify two distinctive metabolic fingerprints in PCa, reflecting their molecular phenotype: phospho-AKT^{high}/MYC^{low} versus phospho-AKT^{low}/MYC^{high} tumors [36]. Interestingly, these oncogene-associated metabolic signatures were independent of Gleason score or pathological stage. Moreover, sarcosine – an N-methyl derivative of glycine, previously identified as an oncometabolite that increased significantly during disease progression from normal to localized to metastatic PCa [37-40] -, was exclusively accumulated in MYC^{high} tumors [36].

Therefore, this study shows how metabolome remodeling associated with the oncogenic transformation of prostate epithelial cells is accompanied by transcriptional changes in key metabolic enzymes. In particular these findings link AKT activation with glycolysis and

other glucose-related pathways, and MYC overexpression with deregulated lipid metabolism.

Finally, both metabolic phenotypes were characterized by a high expression of fatty acid synthase (FASN), the enzyme at the crossroad between aerobic glycolysis and lipid metabolism [41]. This result confirms the multifaceted role of this protein in fine-tuning the balance between different metabolic pathways, regulating the flux of glucose for acetyl CoA generation and ultimately, *de novo* lipogenesis (Figure 1).

The clinical implications of the different prevalence of each cell type characterized by a distinctive metabolic fingerprint are unknown. The largest study performed to examine the prognostic role of MYC in PCa, showed that neither MYC protein overexpression nor MYC mRNA overexpression were strong prognostic factors for this tumor. There were no significant associations between MYC protein expression and stage, grade, or PSA levels [42]. Similarly, a previous study showed that phosho-AKT expression had a limited value as biomarker since it did not provide significant prognostic information especially in patients with Gleason scores 6-7 [43].

Beyond the prognostic significance of MYC-high versus AKT-high tumors, the characterization of these two cellular subtypes and their relative prevalence in the same specimen, could have important diagnostic and therapeutic implications. For example, metabolic imaging techniques such as radiolabelled 2-deoxy-2-[18F]fluoro-D-glucose (18F-FDG) PET could have a better diagnostic performance in AKT-high PCa compared to AKT^{low}/MYC^{high} tumors. Likewise, these findings provide important implications for the development and use of targeted therapies according to prevalent metabolic phenotype.

3. **Novel insights into the prostate cancer metabolome: the lipogenic phenotype of prostate cancer**

The capacity of normal prostate cells to produce and secrete high levels of citrate is related to their capability of accumulate zinc, which inhibits the mitochondrial enzyme aconitase (ACO2) [44-47]. This enzymatic inhibition blocks the tricarboxylic acid (TCA) cycle at the first oxidative reaction, leading to citrate accumulation and inducing a general metabolic adaptation that has important consequences on the cell energy balance.

During neoplastic progression, PCa cells undergo adaptive modifications of their metabolic activities to sustain cellular growth and proliferation [28]. One of the most important events observed in PCa cells is the loss of their ability to accumulate zinc. This alteration is associated with an increased energy efficiency, and a series of metabolic adaptations, including enhanced lipid biosynthesis.

Androgens have a fundamental role in PCa, not only promoting cancer cell growth and survival but also activating both glycolysis and oxidative phosphorylation. In particular, it has been shown that androgens increase mitochondrial function and biogenesis, stimulating the AMPK-PGC1α cascade [48]. AMP-activated protein kinase (AMPK) has an important role in controlling cellular homeostasis by regulating the use of carbohydrates, lipids, and amino acids as energy sources [49]. Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α) is a transcriptional coactivator that acts as a master regulator of mitochondrial biogenesis and function, and has a role in the pathogenesis of some metabolic diseases such as obesity and diabetes [50].

In a recent study, using an integrated multi-omics approach, Shao and colleagues revealed that PCa is characterized by the accumulation of metabolic intermediates and an increased expression of genes in the TCA cycle [51]. These findings are in accordance with the reactivation of ACO2, and the restoration of metabolic flux through the Krebs

cycle. Interestingly, the existence of potential anaplerotic routes from the metabolism of pyruvate, glutamine, and branched chain amino acids, that replenish metabolites for the TCA cycle, was also shown [51]. Increased lipogenesis for cell signaling, membrane formation and cellular proliferation is one of the most significant events in cancer metabolism reprogramming [52]. In PCa an increased expression of choline kinase alpha (CHKA), an enzyme involved in phospholipids bioynthesis, has been demonstrated [53]. In fact, an increased phosphatidylcholine:choline ratio, in association with higher levels of other phospholipids such as phosphatidylethanolamine and glycerophosphocholine, has been demonstrated in PCa, in accordance with an enhanced membrane structural lipids biosynthesis program [53]. Recently, in addition to its well-known function in fueling membrane production through the Kennedy pathway, CHKA has been shown to act as a chaperone that regulates AR signaling, promoting a feed-forward AR-CHKA signaling loop that reinforces AR activity [54]. These findings suggest that CHKA could have a role as a therapeutic target and prognostic marker especially in advanced PCa. In this perspective, a CHKA inhibitor for the treatment of solid tumors is under investigation (ClinicalTrial.gov identifier NCT01215864).

Other metabolic intermediates of de novo lipogenesis, including diacylglycerol (DAG), phosphatidic acid (PA), 6 cholesteryl ester (CE), sphingosine 1-phosphate (S1P), and lysophosphatidic acid (LPA), are significantly increased in PCa tissues, in accordance with their role as second messengers in different signaling pathways regulating migration and invasion [55].

We know that de novo lipogenesis and cholesterogenesis are sustained by conversion in the cytosol of citrate to acetyl-CoA by ATP citrate lyase (ACLY). Other fundamental enzymes involved in the lipid and cholesterol metabolism include acetyl-CoA carboxylase (ACC), fatty acid synthase (FASN), stearoyl-CoA desaturase 1 (SCD1), 3-hydroxy-3-

methyl-glutaryl-CoA reductase (HMGCR), and squalene epoxidase (SQLE). Overexpression of these proteins has been demonstrated in different cancers, especially in PCa where their regulation is under the control of AR.

Cholesterol is a fundamental lipid for plasma membrane integrity, being a precursor of all steroid hormones, and has an important role in signal transduction. Its levels are increased in cancer cells, and the induction of cholesterogenesis has been demonstrated to promote cell growth [56,57]. In this setting, an aberrant accumulation of esterified cholesterol has been observed in lipid droplets of high-grade and metastatic human PCa. This feature was quite specific because it was evident in cancer tissue but not detectable in normal prostate. In particular, cholesteryl ester accumulation in PCa cells was demonstrated to be the consequence of an enhanced uptake of low-density lipoprotein (LDL), being induced by loss of PTEN, upregulation of the PI3K/AKT/mTOR pathway, and the consequent activation of sterol regulatory element-binding proteins (SREBPs) [58]. Similarly, metabolomics analysis of PCa bone metastases revealed increased levels of several amino acids (including sarcosine) and cholesterol. All PCa metastases showed strong LDL receptor (LDLR) staining in epithelial cancer cells, while HMGCR staining was more heterogeneous. Interestingly, higher intensity HMGCR was detectable in endothelial, immune system, and bone cells. The authors suggested that PCa cells in the bone microenvironment could synthesize cholesterol de novo via HMGCR, but also that this metabolite could be synthesized by other cell types expressing HMGRC, and exported and uploaded by cancer cells through LDLR [59]. From a clinical point of view, two recent studies have shown that statins administration was significantly associated with prolonged cancer-specific survival and increased early > 30% PSA declines in a cohort of metastatic PCa patients receiving second-line treatment with abiraterone or enzalutamide [60,61].

SREBPs are basic helix-loop-helix-leucine zipper (bHLH-Zip) transcription factors that bind to the sterol regulatory element (SRE) DNA motif and act as master regulators of lipid and cholesterol biosynthesis. In fact, SRE is present in the promoter regions of genes encoding enzymes for fatty acid, lipid, and cholesterol biosynthesis, including HMG CoA synthase, FASN, SCD1, and LDLR [62].

Huang et al. [63] showed that sterol SREBP-1 induced PCa cell proliferation, migration, and invasion by activating lipogenesis, and an increased production of reactive oxygen species and NADPH oxidase 5 (Nox5) expression. In addition, a recent study showed that SREBP-1 expression, processing and activation was promoted by the AR-mTOR axis, and that SREBP-1 had an important role in the citrate metabolism, regulating the balance between mitochondrial citrate consumption for ATP generation and its usage as carbon source for de novo lipogenesis [64]. In turn, SREBP-1 was able to regulate AR expression by binding to its promoter and sustaining the PCa lipogenic phenotype, stimulating the formation of fatty acids and lipid droplets in cancer cells [63]. In this scenario, two recent studies identified novel genomic drivers of the lipid metabolism in PCa [65,66]. Both studies used the PTEN-null transgenic mouse model which recapitulates the phases of PCa development from high-grade prostate intraepithelial neoplasia (HGPIN) to invasive cancer. The first study explored the role of the pyruvate dehydrogenase complex (PDC) in supporting PCa anabolism [65]. PDC is a multimeric enzyme complex which is responsible for the conversion of pyruvate to acetyl-CoA. It includes a main subunit denominated pyruvate dehydrogenase A1 (PDHA1), which is regulated by pyruvate dehydrogenase phosphatases 1 and 2 (PDP1 and PDP2), that act as PDHA1 activators. Both PDHA1 and PDP1 are frequently amplified at gene and protein level in primary PCa, especially in high grade tumors. The Alimondi group showed that PDC localizes in both the mitochondria and the nucleus, where it controls complementary aspects of lipid metabolism. Nuclear PDC controls the expression of the SREBP1-target genes ACLY and SQLE, through

histone acetylation. In particular, PDHA1 knockdown decreases the levels of acetylated histone H3 Lys 9 (H3K9ac), and reduces the expression of these two rate-limiting enzymes for lipid and cholesterol biosynthesis. In a complementary fashion, mitochondrial PDC provides compounds for lipogenesis, increasing TCA cycle intermediates [65]. In the second study, the Pandolfi group showed that in PCa, a SREBP-dependent lipogenic program was stimulated by the concomitant activation of the MAPK and PI3K-AKT pathways [66]. These authors proposed a model in which PTEN loss drives tumor progression in cooperation with PML loss. In this sense, PML could act as a critical factor involved both in MAPK signaling and lipogenesis inhibition; therefore, its loss could enhance the metastatic potential of Pten-null PCa, inducing hyperactivation of the MAPK pathway, boosting PI3K-AKT signaling and upregulating SREBP-target genes [66].

More recently, Bader et al. showed that the mitochondrial pyruvate carrier (MPC), a critical metabolic conduit linking cytosolic and mitochondrial metabolism, was transcriptionally regulated by AR [67]. In particular, these authors demonstrated in AR-driven PCa models, that AR regulation of the MPC enables glycolytic flux to be funneled directly into mitochondria to fuel the TCA cycle that provides citrate for lipogenesis, reducing equivalents for oxidative phosphorylation and intermediates for amino acid biosynthesis. MPC is significantly increased in primary prostate tumours, it is associated with poor clinical outcomes and represents an intriguing candidate target for PCa therapy. In fact, MPC inhibition using MSDC0160 - a peroxisome proliferator-activated receptor gamma (PPAR-γ)-sparing thiazolidinedione in clinical development - suppresses tumour growth in several preclinical models of hormone-responsive and castrate-resistant PCa. In this setting, MPC inhibition disrupted TCA function, prevented cell cycle progression, and resulted in profound alteration of metabolic homeostasis with resultant impacts on intracellular metabolite pools, reducing potential, ATP content and anti-oxidant capacity [67].

Analysis of fatty acid and cholesterol homeostasis genes in the PCa patient cohort of the TCGA database (PRAD) through the cBioPortal [68], further supports the important role of these metabolic pathways in PCa development (Figure 2 and 3). For example, around 67% of the tumors from 491 PCa patients showed increased gene copy number or expression of fatty acid metabolism genes. Interestingly, analysis of MLYCD revealed deep deletions in approximately 25% of PCa patients. MLYCD encodes for malonyl-CoA decarboxylase, an enzyme that decarboxylates malonyl-CoA to acetyl-CoA, essentially reversing the reaction catalyzed by acetyl-CoA carboxylase.

4. Reciprocal metabolic reprogramming in the tumor-stroma interplay and the role of periprostatic adipose tissue

Cancer cells are able to induce different alterations in their microenvironment by inducing changes in extracellular matrix composition and releasing a series of cytokines and growth factors that support cancer cell survival and proliferation. These molecules also stimulate stromal cells, inducing their epigenetic reprogramming, and modify their mutual interaction with cancer cells to meet the metabolic requests of these latter. This remodulation of the crosstalk between cancer and stromal cells creates a positive loop that supports cancer cells proliferation in a hostile environment, and enhances their ability to infiltrate and metastasize.

In this regard, cancer-associated fibroblasts (CAFs) and tumor-associated macrophages (TAMs) actively interact with PCa cells through a reciprocal interplay. Indeed, we can recognize an “efferent” pathway, in which cancer cells induce a reactive response in the

stroma, mainly through the secretion of pro-inflammatory cytokines, and an “afferent” pathway, in which CAFs and TAMs contribute to regulate the cancer cell response [69,70].

This two-compartment crosstalk among cell populations within the tumor mass goes beyond the ability of CAFs to induce the epithelial–mesenchymal transition and stem-like traits in PCa cells to include also mutual metabolic reprogramming. In particular, Lisanti's group proposed a new model of metabolic symbiosis, called the “Reverse Warburg Effect”, describing a host-parasite type of relationship in which CAFs could directly feed the epithelial cancer cells, providing the necessary energy-rich metabolites [71]. In this scenario, the existence of metabolic reprogramming of CAFs toward a Warburg phenotype has been demonstrated, that occurs because of an intercellular contact with PCa cells [72].

This interaction activates CAFs, induces the expression of glucose transporter GLUT1 in these cells, enhances lactate production, and promotes the exportation of lactate through the de novo expression of monocarboxylate transporter-4 (MCT4). On the other hand, PCa cells, upon contact with CAFs, are reprogrammed toward an aerobic metabolism, featuring a reduced GLUT1 expression and an increased lactate import via the lactate transporter MCT1 . The lactate can then enter the TCA cycle, making PCa cells gradually independent of glucose consumption, while developing a dependence on lactate import for anabolic pathways and cell proliferation [72].

The efficacy of this reciprocal metabolic reprogramming through a lactate shuttle has been demonstrated also in urothelial bladder cancer. Interestingly, in this tumor the existence of a 3-compartment metabolic coupling has been proposed [73]. According to this model, catabolic hypoxic cancer cells and catabolic stromal cells express MCT4, and are coupled to anabolic normoxic cancer cells that express MCT1. Therefore, glycolysis-derived lactate is exported through MCT4 from catabolic cells (both cancer cells and CAFs), and uploaded

through MCT1 into anabolic cells, where it fuels mitochondrial respiration and malignant proliferation.

This co-evolution of cancer and stromal cells involves not only CAFs, but also other cellular elements such as adipocytes. Obesity and high visceral fat have been associated with an increased risk of PCa progression to metastatic disease [74]. The obesity-related drivers that may support the increased aggressiveness of PCa cells include an excess fatty acids dietary intake, alterations in the insulin and IGF-1 axis, and higher levels of pro-inflammatory cytokines [26]. Previous studies have shown that mice with total body inactivation of the autophagy substrate p62/SQSTM1 develop mature-onset obesity, leptin resistance, as well as impaired glucose and insulin tolerance [75]. In addition, the selective inactivation of p62 in adipocytes led to an impaired mitochondrial function in brown adipose tissue, recapitulating the adipose tissue expansion observed in total knockout mice [76]. Therefore, to study the specific crosstalk between adipocytes and PCa cells, Huang and colleagues used a TRAMP^{+} mouse model of PCa in which p62 in adipocytes was selectively inactivated (TRAMP^{+}/p62^{adipo} model) [77]. First of all, it was shown that TRAMP^{+}/p62^{adipo} mice exhibited an increased adiposity and developed PCa with more aggressive characteristics, featuring a higher incidence of visceral metastases compared to TRAMP^{+}/WT controls. p62 inactivation in adipose tissue resulted in the repression of energy-consuming pathways such as lipogenesis and oxidative phosphorylation through the reduced activation of mTORC1, which regulates lipid metabolism via SREBP1. This control of metabolic activities in adipocytes could serve as a strategy to save energy compounds for use by tumor cells. In fact, in contrast to the repression of the fatty acid metabolism in adipocytes, PCa cells showed an enrichment of genes involved in fatty acid β-oxidation, in association with the upregulation of carnitine palmitoyltransferase 1A (CPT1A). CPT1A is a rate-limiting enzyme involved in the transport of long-chain fatty acids for β-oxidation, and it is overexpressed in various tumors, including PCa. In addition,

p62 inactivation in adipose tissue was associated with the induction of the epithelial-mesenchymal transition in cancer cells, which is in line with the increased number of visceral metastases observed in TRAMP^{+}/p62^{adipo} mice. In particular, p62 loss generated an intensified inflammatory response in adipose tissue and an increased expression and secretion of osteopontin by adipocytes. Subsequently, osteopontin drives tumor migration and invasion, inducing the expression of CPT1A in cancer cells. Taken together, these findings demonstrate that a p62 deficiency in adipose tissue represses nutrient-utilizing pathways and upregulates the expression of osteopontin in adipocytes, which enhances the fatty acid metabolism in PCa cells via CPT1A expression, promoting cancer proliferation, invasion, and metastasization [77] (Figure 4).

Adipose tissue and, in particular, the visceral fat depot, is metabolically active and has a unique inflammatory profile [78]. In this setting several mechanism have been proposed to explain the obesity-cancer association, including the presence of cancer-associated adipocytes, adipokines, obesity-related inflammatory cytokines production, and alteration in the metabolism of sex hormones. Recent studies have demonstrated that an increased thickness of the adipose tissue surrounding the prostate (periprostatic adipose tissue – PPAT) was positively associated with PCa progression and the presence of high-grade disease [79-83].

Finley et al, [84] analyzed for the first time the adipokines levels in the PPAT and found that their tissue concentrations were increased compared with serum values. In particular, they found that interleukin-6 (IL-6) levels in PPAT conditioned medium were extremely high and these values correlated with pathological grade. This finding was further extended by cell signaling analysis that showed an increased phosphorylation of STAT3 in high grade tumors, suggesting that PPAT may have a role in modulating PCa aggressiveness by serving as a source of IL-6.

A recent study has shown that tumor-surrounding adipocytes exhibit phenotypical changes, characterized by reduction of the lipid amount and down-regulation of adipocyte markers expression, in association with over-production of pro-inflammatory cytokines and extracellular matrix-related molecules [85]. This crosstalk allows cancer cells to induce lipolysis in adypocites, with release of free fatty acids that are transferred to PCa cells. In tumor cells free fatty acids induces oxidative stress through the expression of a pro-oxidant enzyme, the NADPH oxidase 5 (NOX5). The increased ROS production activates the HIF1/MMP14 pathway, which contributes to the tumor cell invasion ability. Furthermore, they showed that this lipolytic process with the associated signaling pathway in PCa cells, was particularly upregulated at the tumor-invasive front [85]

Several evidences have suggested an important role of the PPAT chemokines in creating a specific microenvironment for PCa cells survival and invasiveness. Chemokines are small cytokines with a chemotactic activity, which are involved in different processes, from recruitment and activation of leukocytes to regulation of cancer cells migration. One of the chemokines promoting cancer progression is CXCL12/SDF-1, which is able to activate signaling events through two different receptors, CXCR4 and CXCR7. Saha et al. showed that CXCL12 signaling mediates obesity-induced PCa progression in a mouse model of PCa. Moreover, they demonstrated that CXCL12 also activates many oncogenic signaling pathways including STAT3, NFκB and MAPK, suggesting that in obesity-driven PCa, CXCL12-CXCR4/CXCR7 signaling axis may represent a potential target for offsetting the effect of obesity on PCa progression [86,87].

In a previous study, Laurent et al. [87], investigated the importance of another chemokine secreted by adipocytes. They showed that the increased secretion of CCL7 by adipocytes, promotes the extraprostatic extension and local dissemination of PCa. In particular, it was shown that CCL7 produced by mature adipocytes, diffuses from PPAT to the peripheral

zone of the prostate, interacting with CCR3 receptor that is overexpressed in tumor cells. Activation of CCL7-CCR3 axis induces chemotaxis of PCa cells and this effect is enhanced by obesity [87].

5. Targeting metabolism for prostate cancer therapy

One of the key opportunities of the metabolic reprograming that occurs in cancer is that such changes provide a wide platform for different therapeutic strategies. Although these alterations may not represent critical survival factors for all cancer cells, targeting these metabolic pathways in association with standard therapies may provide a tool to overcome resistance mechanisms. Some metabolic targets in cancer cell includes proteins of glucose metabolism, serine biosynthesis and folate cycle, glutaminolysis, TCA cycle, oxidative phosphorylation and electron transport chain [88,89].

Dysregulated lipid metabolism is a distinctive feature of PCa, and fatty acids availability can be limited blocking their synthesis, increasing their degradation, diverting them to storage, or blocking their release from depository [90]. Some inhibitors targeting lipid metabolic pathways are summarized in Table 1.

Moreover, in recent years immune checkpoint blockade using antibodies targeting cytotoxic-T-lymphocyte-associated protein 4 (CTLA4) or programmed cell death 1/programmed cell death 1 ligand 1 (PD1/PD-L1) have shown effective and durable therapeutic responses in a significant subset of patients across a variety of cancer types, including PCa [91]. Recent evidences have shown that tumor microenvironment supports inappropriate metabolic reprogramming that impairs tumor-infiltrating lymphocytes (TILs) function, and therefore affecting the response to immunotherapies. In particular tumor microenvironment is characterized by a reduced availability of carbon sources critical for

TILs function, and accumulation of oncometabolites with an immunosuppressive role such as kynurenine [92].

In this scenario, targeting tumor cell metabolism becomes an attractive strategy not only for anti-tumor immunity restoration but also for the enhancement of immunotherapies.

6. Expert Opinion

Recent discoveries in cancer metabolomics have provided novel insights into pathways that regulate the PCa cell metabolism, with the aim of better classifying this disease and identifying new diagnostic and prognostic markers.

Because of the low specificity of prostate specific antigen (PSA), more than 70% of men with PSA levels in the grey zone have a negative first biopsy. PSA is not a cancer-specific biomarker, therefore we need to identify novel molecular factors to improve early detection, risk assessment, the prediction of clinical outcome, and treatment response [8,37-40,92,93]. Integrated multi-omics analysis of tumor samples has led to the discovery of different biomarkers although none of these is currently recommended in clinical practice [51,89].

The recent identification of a potential diagnostic role of some metabolites such as sarcosine, kynurenine, or cholesteryl oleate, as well as the expression of metabolic enzymes involved in specific pathways, may improve cancer detection and prognostication [37-40, 55, 92]. In addition, the evidence of different metabolic phenotypes with a differential preferential activation of the glucose-related metabolism or of lipogenic pathways opens new perspectives for a metabolic classification of PCa, aimed at better identifying specific therapeutic targets [36]. The overexpression in PCa of enzymes

involved particularly in lipogenic pathways, such as SREBP1, ACLY or FASN, makes them attractive targets for therapeutic intervention.

For example, the pharmacological inhibition of SREBP1 by fatostatin alters the balance between lipid biosynthesis and mitochondrial respiration in PCa cells, rewires the citrate metabolism towards oxidative phosphorylation, and impairs lipid accumulation [64]. Considering the relationship between de novo lipid synthesis, intracellular lipid storage, and metastasis, SREBP1 inhibition may offer an attractive pharmacological approach in advanced disease.

Interestingly, the pharmacological inhibition of PDC using 3-fluoropyruvate decreased tumor cells proliferation and arrested cancer growth in human PCa xenograft models [65].

Moreover, considering that alterations of cholesterogenesis and related enzymes seem to have an important role in cancer development and progression, the use of statins or squalene synthesis inhibitors, in association with chemotherapy or targeted drugs, might be particularly effective in a subgroup of PCa patients. In fact, two recent studies have shown that statins (HMGCR inhibitors) use was associated with an increased cancer-specific survival in a cohort of metastatic PCa patients treated with second-line abiraterone or enzalutamide [60,61].

Although many epidemiological studies support a role for increased BMI and obesity as risk factors for poor outcome in men with PCa, there are still gaps in our knowledge that need to be investigated to understand the molecular basis of this phenomenon. Interestingly, although obesity is associated with an increased risk of death [95], there are conflicting studies about the relationship between obesity and mortality in patients with several chronic diseases, including cancer. In particular, among patients affected by cancer, obesity has been associated with improved survival compared with normal-BMI patients, suggesting that obesity could have a protective role. This phenomenon has been

termed the “obesity paradox” and it has been observed also in PCa patients. Schiffmann et al. showed in a population of 13,667 PCa patients, that increased BMI (≥ 30 Kg/m^2) was associated with a decreased risk of metastases after radical prostatectomy [96].

Different mechanisms have been proposed to explain this phenomenon, including a protective effect of statins in high BMI patients. In a recent publication, Shachar et al. suggested to examine body composition beyond BMI and to use other body composition parameters to better stratify patients in risk groups and develop individualized strategies [97].

A recent study has defined metabolic and genetic signatures of obesity by using non-targeted metabolomics and whole-genome sequencing [98]. The authors identified the profound perturbation of metabolome in association with BMI and demonstrated that metabolite levels were able to predict obesity status. In addition, they described a model based on the metabolite signature (mBMI) more accurate than the actual BMI in health risk stratification [98].

Accumulating evidence has highlighted the importance of metabolomic technologies and in particular of lipidomics for exploring novel pathogenetic pathways in PCa.

This approach will lead in the next years to innovative strategies in diagnostic and therapeutic settings:

1. The definition of the PCa metabolome will enable the identification of metabolic signatures that may serve as biomarkers to distinguish potentially aggressive PCa from indolent disease.

2. Metabolic imaging using lipid precursor tracers or other metabolomics-based compounds will be a more sensitive and specific tool for disease diagnosis and follow-up

3. The identification of neoplastic subclasses based on particular metabolic alterations will introduce precision medicine-based approaches for the specific treatment of particular tumor subgroups.

4. A better understanding of the mechanisms involved in metabolic adaptations of cancer cells and of the cross-talk between tumor cells and the surrounding stroma should lead to the identification of novel and more specific therapeutic targets.

Some of these innovations are certainly too optimistic, especially in a five-year perspective, however most recent studies are focusing on identification of the genomic drivers of PCa metabolism, providing implications for a more precise subtyping and innovative treatment of this tumor. Many compounds such as ranolazine (a CPT1 inhibitor) or orlistat (a FASN inhibitor) are FDA approved drugs, and their introduction in clinical practice will expand in the next year the therapeutic armamentarium for the treatment of PCa.

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Declaration of interest

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Table 1: Examples of lipogenesis and cholesterogenesis inhibitors

Target	Inhibitor	Comments
Acetyl-CoA carboxylase (ACACA)	Soraphen A	Inhibition of FA synthesis and stimulation of FA oxidation
	A-769662	
	5-(tetradecyloxy)- 2-furoic acid (TOFA)	
ATP citrate lyase (ACLY)	SB-204990	
Acyl-CoA synthetase (ACSL)	Triacsin C	inhibitor of ACSL1, 3, and 4
	Thiazolidinediones (TZDs)	inhibitor of ACSL4. Activation of PPAR-□
Acylglycerolphosphate acyltransferase 2(AGPAT2)	CT-32501	
Choline kinase alpha (CHKA)	MN58B	
	TCD-717	

Fatty acid synthase (FASN)	Orlistat	FDA approved drug
	Cerulenin	
	C75	Cerulenin derivative
	C93	
	C247	
Carnitine palmitoyl transferase 1 (CPT1)	Etomoxir	
	Ranolazine	FDA approved drug
	Perhexiline	
Monoacylglycerol lipase (MGLL)	JZL184	
	URB602, URB754,	
Stearoyl-CoA desaturase (SCD)	BZ36	
	A995572	
Sterol response element binding protein-1 and -2 (SREBP1-2)	Fatostatin	
	FGH10019	
3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMGCR)	Statins	

Figures

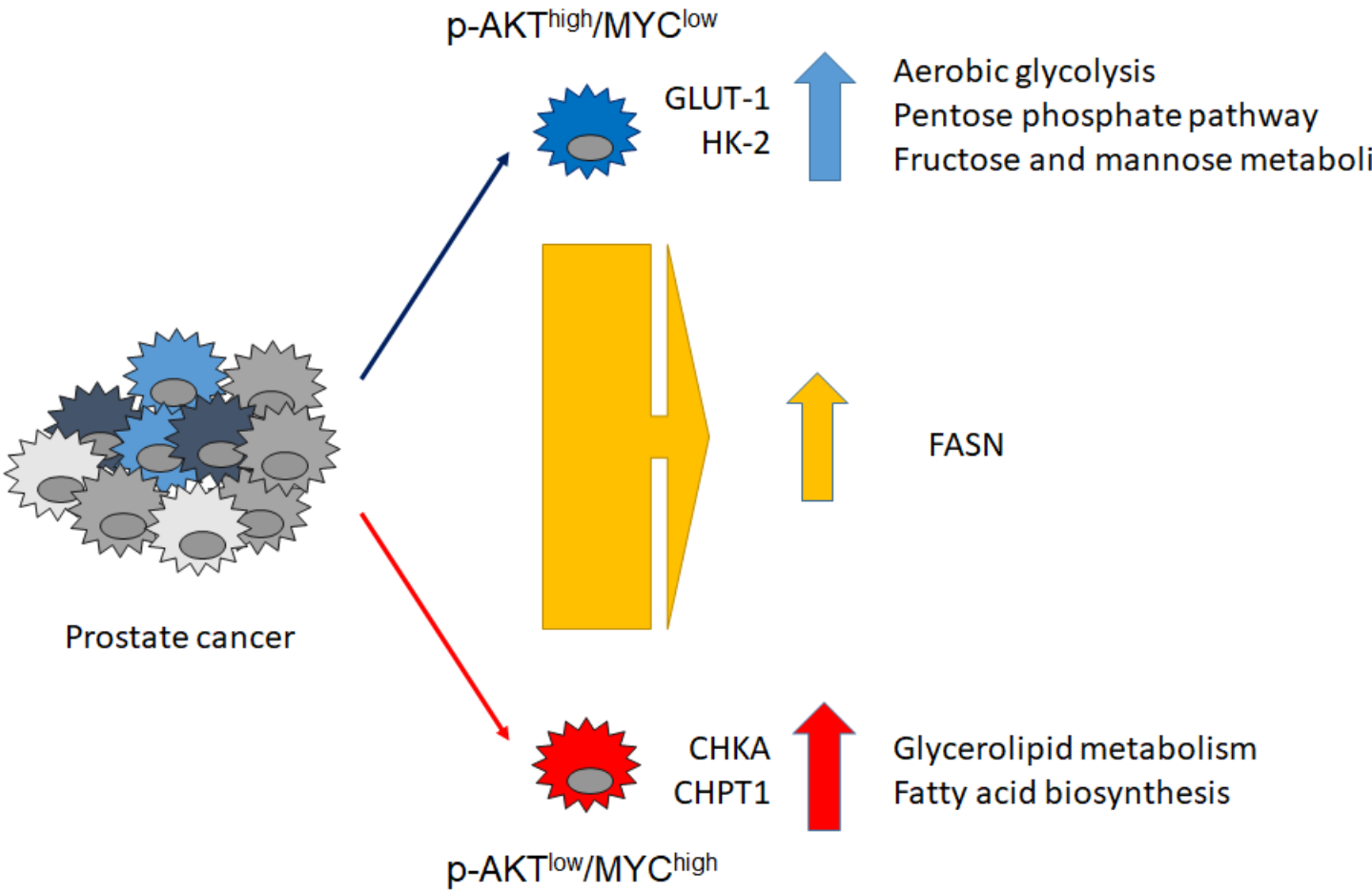

Figure 1: Evidence of two distinctive metabolic signatures in prostate cancer. CHKA: choline kinase alpha; CHPT1: Choline phosphotransferase 1; HK2: hexokinase 2; GLUT1: glucose transporter 1.

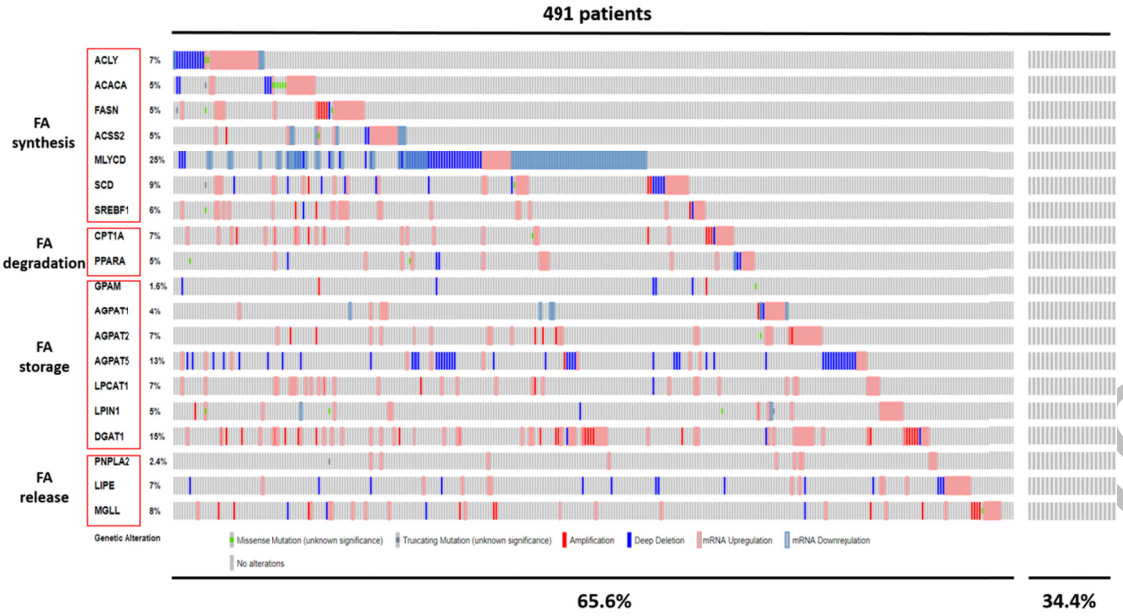

Figure 2: Oncoprints of fatty acid (FA) metabolism genes in the cancer genome atlas (TCGA) PCa patient cohort (PRAD). About 65%of the tumors from 491 patients in PRAD showed altered gene copy number or expression of FA metabolism-related genes.

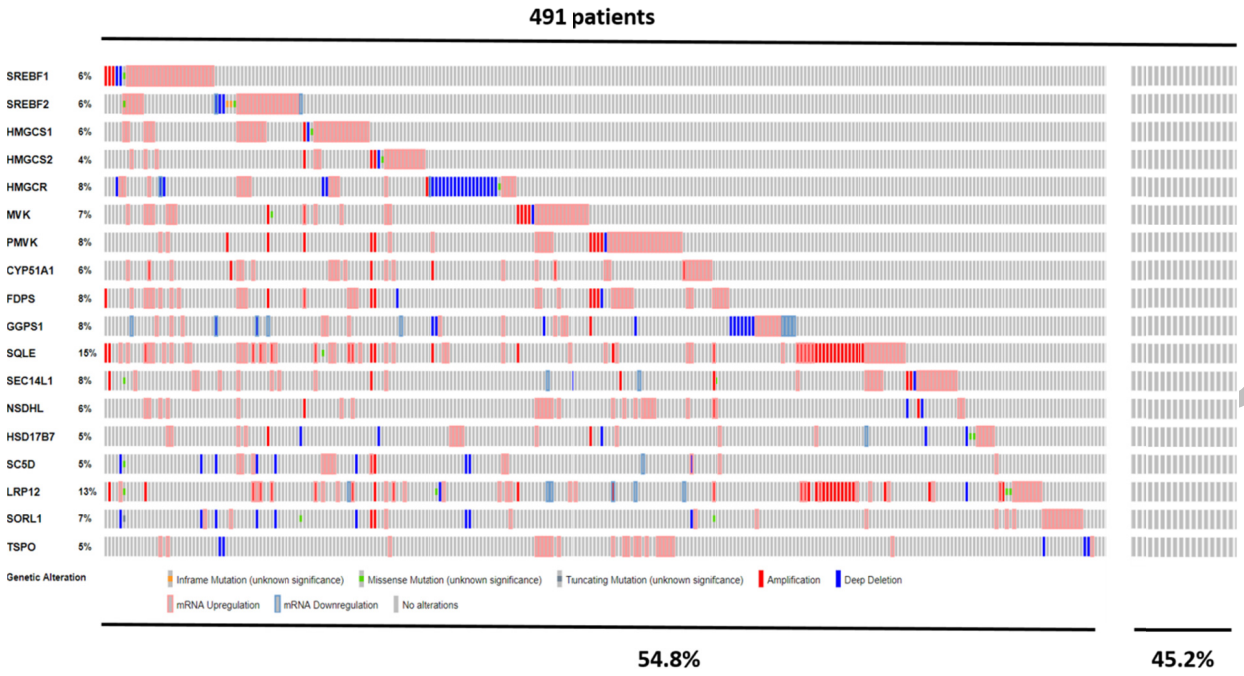

Figure 3: Oncoprints of cholesterol homeostasis genes in the cancer genome atlas (TCGA) PCa patient cohort. About 55% of the tumors from 491 patients in PRAD showed altered gene copy number or expression of cholesterol synthesis genes.

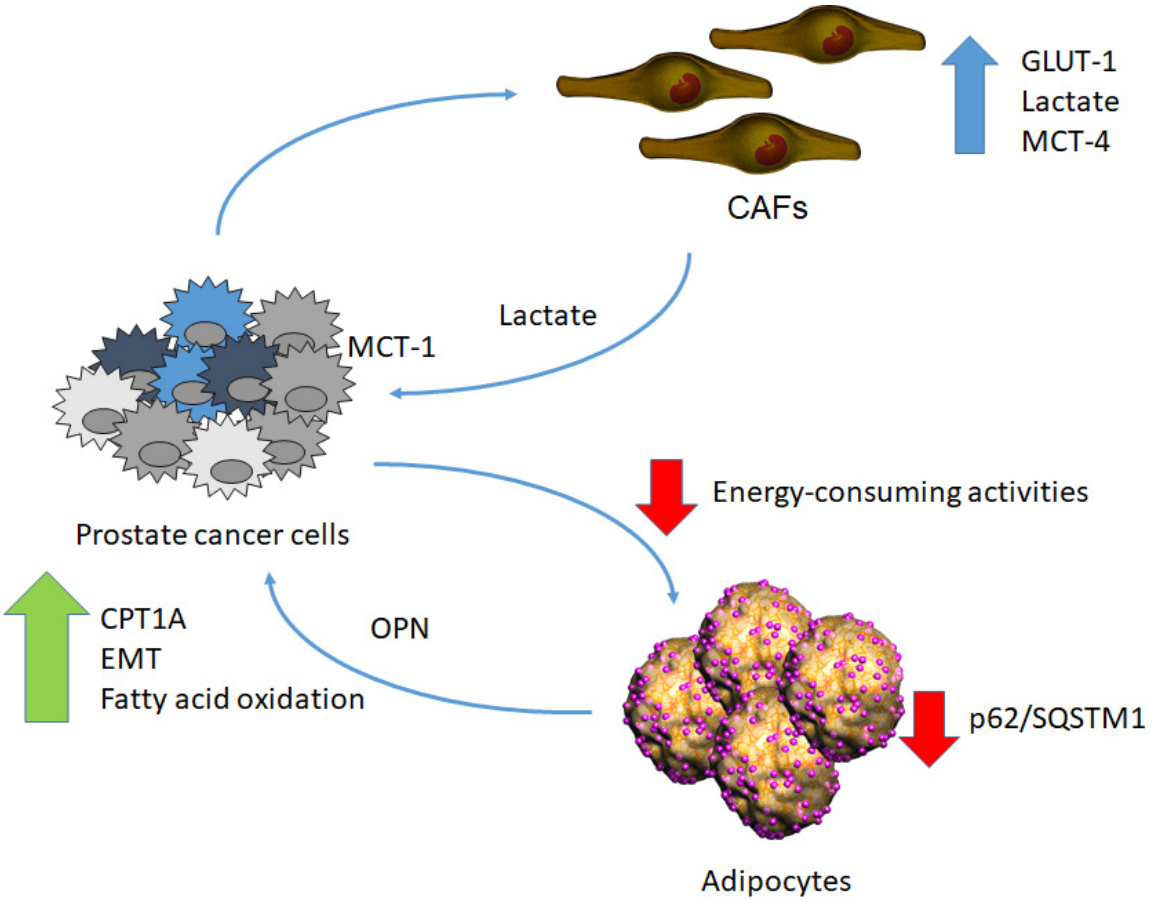

Figure 4: Reciprocal metabolic reprogramming in the tumor-stroma interplay. Cancer cells induce the expression of glucose transporter GLUT1 in cancer-associated fibroblasts (CAFs), enhances lactate production, and promotes the exportation of lactate through the de novo expression of monocarboxylate transporter-4 (MCT4). On the other hand, cancer cells increase lactate import via the lactate transporter MCT1. p62 deficiency in adipose tissue represses nutrient-utilizing pathways and upregulates the expression of osteopontin (OPN) in adipocytes, which enhances the fatty acid metabolism in cancer cells via carnitine palmitoyltransferase 1A (CPT1A) expression, promoting epithelial-mesenchymal transition (EMT) and cancer aggressiveness.