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ALTERED SIGNALING PATHWAYS IN PROSTATE CANCER DRIVE METABOLIC FATE

Oncology

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ABSTRACT

Prostate cancer is one of the leading causes of men death worldwide. Several signaling pathways are highly implicated in the progression of this disease. Interestingly, variations in a single gene can orchestrate changes in a metabolic pathway and thus, confer an adaptive advantage. Metabolic reprogramming has emerged as one of the hallmarks of cancer and arises as consequence of changes in critical signaling pathways provoked by balance disruption between oncogenes and tumor suppressors expression. Therefore, metabolomic analyses provide relevant information that is not available with only genomic or proteomic studies. Noticeably, basal energetic status in luminal epithelial cells of the prostate gland contrasts with other tissues since Krebs cycle is altered so as to generate high citrate levels achieving a more glycolytic phenotype. Furthermore, the altered signaling pathways in prostate cancer depict changes in cellular metabolism that support the demands of rapid cell division. Particularly, metabolic pathways significantly altered in this malignancy are glutaminolysis and lipid metabolism that contribute directly to the production of acetyl-CoA and NADPH required for the synthesis of fatty acids. Therefore, deciphering the metabolic rewiring propelled by signaling pathways dysregulation is vital for the development of new therapeutic approaches in prostate cancer. Advances in these fields highlight the importance of changes in energetic metabolism during the progression to castration resistant prostate cancer and bone metastases.

KEYWORDS

1. Introduction

Prostate cancer (PCa) is the second leading cause of cancer death in men in the United States.[1] While most of the cases diagnosed in early stages are localized and can be cured, others will progress to metastatic disease and eventually, after androgen deprivation therapy (ADT), will resume and become castration-resistant (CRPC). Bone is the most frequent site of PCa progression[2], being metastases the main cause of morbidity and mortality of the disease.[3] Tumor heterogeneity in primary prostate cancer is a well-established phenomenon. For this reason, it is critical to understand the misregulation of gene expression and the impact on the metabolic outcome that promotes bone prostate cancer progression.

The complexity of this multigenic disease is characterized by a diversity of genetic and epigenetic alterations.[4,5] Currently, our view of cancer has evolved to include a dysregulation in metabolism in addition to the transformed cells that have re-arranged oncogenic signaling pathways.[4,6,7] All major tumor suppressors and oncogenes have intimate connections with metabolic pathways.[6,8] Most tumors display oncogene-driven reprogramming of several metabolic pathways, which are pivotal to sustain their growth and proliferation. Interestingly, variations in a single gene can orchestrate changes in a metabolic pathway and thus, confer an adaptive advantage.

The intricacy of the signaling networks in advanced prostatic disease, highlights that restricting one pathway might cause uncertain responses.[9] Therefore, metabolomic analyses provide relevant information unavailable with genomic or proteomic studies and determine the characteristics of the tumor progression. Altogether, deciphering the altered metabolic pathways in prostate carcinogenesis and prompting them as targets for therapy, open several key avenues for future clinical application.

2. Signaling pathways altered in prostate cancer

2.1. *Oncoproteins*

Androgen receptor signaling. The androgen receptor (AR) signaling pathway has been therapeutically targeted for years in patients who are castration-sensitive and in those who develop CRPC. The AR is a nuclear receptor, a transcription factor that mediates the signals of diverse fat-soluble hormones.[10] Notably, AR can orchestrate gene expression either by interacting with androgen response elements (AREs) of target genes or indirectly by activating other growth factor signaling pathways.[10]

Lowering serum dihydrotestosterone (DHT) levels triggers a feedback loop that spikes transcription of the AR in PCa cells.[11,12] This action is thought to cause DNA strand breaks, responsible for the AR amplifications.[12,13] Mutations in the AR itself are less common than amplifications and are described in up to 18% of biopsy samples from patients with CRPC.[14]

As evidenced, there has been a plethora of studies pinpointing the role of the AR in the establishment and progression of PCa. Of note, the AR exerts a key action in the metabolic shift that occurs during progression, modifying the expression of several mediators in the catabolic and anabolic routes. Massie *et al*. demonstrated that PCa cells stimulated with androgen increase glucose consumption and lactate production, with no effect on oxygen consumption rate (OCR).[15] In addition, the meta-analysis of clinically expressed AR targets, revealed that CAMKK2 (calcium/calmodulin dependent protein kinase kinase 2) is overexpressed in PCa. CAMKK2 is a crucial effector of the AR, modulating the glycolytic flux by triggering AMPK signaling.[15] Advanced genomic studies have unveiled an orchestrated network of transcriptional modifications led by the AR which include upregulation of (1) glucose consumption and glycolysis (e.g., GLUT1 [SLC2A1, solute carrier family 2 member], HK2 [Hexokinase 2] and PFKFB2 [6-Phosphofructo-2-Kinase/Fructose-2,6-Biphosphatase]); (2) biosynthetic pathways (e.g., FASN [fatty acid synthase] and ACACA [acetyl-coenzyme A carboxylase alpha]); (3) master modulators of some metabolic processes (e.g., mTOR [mechanistic target of rapamycin] and CAMKK2).[15] In an indirect way, the AR can affect epigenetic activity, redox status and DNA metabolism, as a result of the one-carbon metabolism, being all of these processes hallmarks of cancer.[16] One-carbon metabolism entails the transfer of methyl groups to various intermediates of the folate, methionine, polyamine and transsulfuration routes. Methyl groups are utilized in the nucleotides and polyamines synthesis and additionally, in DNA and protein methylation mechanisms.[17]

AR cofactors. A range of cofactors alters the expression of AR downstream targets.[14] These comprise the transcription factor GATA2, the forkhead protein FOXA1, and the P160 steroid receptor co-activator proteins named NCoA 1, NCoA 2 and NCoA 3. Of note, *AR* cofactor mutations have been observed in both primary and metastatic tumors, while *AR* mutations are solely found in CRPC biopsy samples.[18,19] *AR* alterations and AR cofactor mutations represent almost 70% of aberrations in patients with PCa.[20]

FOXA1 binds to the AR delineating new AR binding sites[21] and in an additional way, regulating metastatic potential in an AR independent manner.[14,22] GATA2 colocalizes with FOXA1 and the AR, promoting the AR expression.[23] NCoA proteins function as steroid receptor co-activators, even with no circulating androgens and NCoA 1 or NCoA 2 overexpression can lead to augmented AR trans-activation.[24] NCoA 2 is amplified in roughly 6% of patients with advanced-stage PCa[25] while NCoA 3 overexpression is linked to hiperproliferation.

PI3K pathway. The PI3K (phosphatidylinositol 3-kinase) pathway is one of the most commonly deregulated signal transduction pathways in PCa patients. This axis controls proliferation, survival, metabolism, angiogenesis, and immune function. PI3K activation results in the catalytic conversion of phosphatidylinositol 4,5-biphosphate [PtdIns(4,5)*P*2] into phosphatidylinositol 3,4,5-triphosphate [PtdIns(3,4,5)*P*3] which, in turn, activates Akt.[26,27] Akt phosphorylates and activates mTOR, a serine/threonine kinase that regulates cell growth.[28] Hyperactivation of this axis by PTEN (phosphatase and tensin homolog) loss, is the most common PI3K alteration observed in patients with PCa (as described below).[29] PTEN encodes a lipid phosphatase that converts PtdIns(3,4,5)P3 into PtdIns(4,5)P2 thus functioning as a negative regulator of PI3K signaling. Conversely, PTEN loss is linked to hormone resistance and insensitivity to chemotherapy. In this sense, high phospho-Akt-1 expression has been demonstrated to be an independent prognostic marker in patients with Gleason scores of 6 and 7.[30]

TMPRSS2-ERG rearrangement. Gene fusions involving TMPRSS2 (transmembrane protease, serine 2) and ETS family transcription factors are frequent in PCa. The most common fusion occurs between TMPRSS2 and ERG [v-ets erythroblastosis virus E26 oncogene homolog (avian)], in roughly 50% of clinical PCa.[31] The androgen response elements, located in the TMPRSS2 promoter region, make TMPRSS2 androgen inducible[32] and thus, fusion with ETS leads to its overexpression. Approximately 90% of PCa with ERG overexpression present the TMPRSS2:ERG fusion, demonstrated to be an early event in the development of the disease.[33] Next-generation sequencing studies suggest that ETS-positive and ETS-negative tumors harbor significant structural differences in their genomes, with ETS-positive cancers having more rearrangement chains (manifestations of chromoplexy) than ETS-negative cancers.[34] Two other recognized gene fusions causing ERG overexpression are SLC45A3:ERG (solute carrier family 45, member 3) and NDRG1:ERG (N-myc downstream regulated 1), with frequencies being less than 5%.[35]

PTEN protein loss occurs in almost half of PCa, usually through genomic deletion, being more commonly detected in ETS-positive cancers.[36] Genetically engineered mice that express ERG or ETV1 under the probasin promoter, develop moderate dysplasia.[37] However, when crossing these mice with PTEN *knock out* mice, ERG or ETV1 facilitate progression of HPIN (high-grade prostatic intraepithelial neoplasia) to invasive adenocarcinoma.[37]

Notably, the master transcriptional regulators of PCa progression, AR and the ETS gene fusions seem to regulate the metabolic signature in the different stages of the disease. Using a combination of high-throughput liquid-and-gas-chromatography-based mass spectrometry, Sreekumar *et al.*, demonstrated that AR and ETS gene fusions directly regulate the levels of sarcosine (an N-methyl derivative of glycine) by transcriptional control of its regulatory enzymes.[38] Metastatic samples showed markedly increased sarcosine in 79% of the specimens analyzed, whereas 42% of the primary adenocarcinoma samples revealed enhanced levels of this metabolite, which were absent in the benign samples. Interestingly, androgen treatment in VCaP (ERG-positive) and LNCaP (ETV1-positive) PCa cells provoked a significant increase in glycine-N-methyltransferase (GNMT) expression and a concomitant decrease in sarcosine dehydrogenase (SARDH) levels.[38] These findings provide evidence of an association between the sarcosine pathway and the AR and ETS gene fusion regulation, two crucial mediators of PCa progression.

To address the target genes deregulated by the *TMPRSS2-ERG* fusion Ribeiro *et al*. performed genome-wide mRNA expression analysis on prostate samples carrying or not the rearrangement. Multiple genes encoding metabolic enzymes or extracellular/transmembrane proteins involved in signal transduction pathways, cell adhesion or matrix remodeling were detected to be co-regulated with ERG.[39] Within the metabolic enzymes list, the authors found deregulation in *GLDC* (with function in amino acid metabolism), *B3GAT1* (with a key role in carbohydrate metabolism), *PLA1A* and *PLA2G7* (involved in fatty acid and steroid metabolism) and *DNASE2B* (with an important role in nucleic acid metabolism).[39]

WNT pathway. The complexity of the signaling cascades in advanced PCa may cause unpredictable outcomes when impairing one specific pathway;[9] in particular when tumor cells need to compensate for the effects of AR inhibition.[40,41] The Wnt/β-catenin axis rises as one of the major pathways involved in developing CRPC since it interacts with the AR.[42] It has been reported that an activating mutation of β-catenin in mouse prostate facilitated sustained prostatic growth after castration.[43] Genome sequencing (RNA-seq and whole exosome sequencing) of CRPC tumors unveiled drastic genomic alterations in multiple components of the Wnt pathway, whereas, no such alterations were observed in hormone treatment naïve PCa.[18,44] The Wnt pathways can be classified into two groups depending on whether or not ligands signal through β-catenin, an intracellular transcriptional co-activator. In patients with localized PCa decreased levels of nuclear β-catenin predict for a poorer prognosis.[45]

The Wnt/β-catenin signaling axis is associated also with insulin secretion and energy balance. Oncogenic signaling pathways modulate the production of energy and macromolecules synthesis that serve as fuel for tumor proliferating cells. Evidence show the participation of Wnt in the reprogramming of cancer cell metabolism and its signaling axis as mediators of tumor bioenergetics.

Caveolin-1 (Cav-1) found in vesicular structures called caveolae was identified as a marker of aggressive PCa.[46] It can bind to lipids and mediate cholesterol and fatty acid metabolism inducing biological responses in a paracrine manner. Interactions between Cav-1 and LRP6 (low density lipoprotein reeptor-related protein 6) were reported to be important for the regulation of Wnt-β-catenin signaling. Tahir *et al.* demonstrated that Cav-1 silencing, down-regulated total and phosphorylated levels of LRP6 in PCa cells under the constitutive expression of Wnt.[46,47] Additionally Cav-1 interacted with LRP6 and activated IGF-IR/IR axis, which in turn lead to aerobic glycolysis mediated by Akt–mTORC. These findings imply a Warburg effect in PCa.

Wnt signaling provides cancer cells with metabolic flexibility, enabling them to sense changes in the tumor microenvironment and reprogram their metabolism accordingly. Hence, as the final cell response to Wnt stimulation is determined by Wnt network interactions that are context specific, directly impacting on patient outcome.[48]

c-MYC. Somatic genomic amplifications of 8q24 are frequent in PCa. This genomic region contains, among other genes, the oncogene *c-MYC* (v-myc avian myelocytomatosis viral oncogene homolog) that is overexpressed in PCa. However, most studies reported a lack of correlation between genomic amplification and *c-MYC* gene and protein expression[49,50] suggesting a regulation at transcriptional and/or translational levels. While some authors described overexpression of c-MYC in primary and metastatic PCa compared to non-tumoral prostatic tissues[49] others reported a negative correlation between c-MYC expression and PCa stage and Gleason score.[50] Interestingly, both studies found that c-MYC expression was lower in high-grade tumors.[49,50] They hypothesized that the lower expression of c-MYC protein in those tumors might be related to the induction of apoptosis caused by initial high levels of c-MYC, generating a selective pressure for tumor cells expressing low/medium levels of this gene.[51]

This protein is a transcription factor that regulates a wide spectrum of cellular processes that include metabolic pathways. Many of the c-MYC-regulated metabolic genes overlap with AR-regulated genes.[52] Some metabolic genes regulated by c-MYC in PCa are GLUT1, HK2 and GLS1 (Glutaminase 1).[52] O'Connell *et al.* showed that overexpression of c-MYC directly activates metabolic enzymes mainly involved in nucleic acid and amino acid biosynthesis.[53] Therefore, c-MYC overexpression might shift the cellular metabolism from the Krebs cycle to the biosynthesis of nucleic acids and proteins, a well-known feature of tumoral cells.

BRCA1 and BRCA2. *BRCA1* and *BRCA2* genes help to maintain genomic stability as they sense DNA damage and promote double strand breaks repair *via* the homologous recombination pathway. Therefore, impaired BRCA1/2 function due to deleterious mutations results in chromosomal instability and less efficient cell cycle arrest and apoptosis. Germline mutations in these genes increase the risk of developing different types of tumors, including PCa, and are inherited in an autosomal dominant fashion with incomplete penetrance.

Mateo *et al*. recently reviewed the prevalence and clinical significance of mutations in DNA repair genes from four different genomic studies performed on PCa tissue.[54] Overall, the frequency of BRCA1 deleterious mutations in the tumors was 0-1.8% for localized PCa and 0-0.7% for CRPC metastasis. BRCA2 was mutated in 0-9.1% of localized PCa and in 12-13.3% of metastatic CRPC[54]. The higher frequency of BRCA2 mutations in CRPC metastasis might be suggestive of a more aggressive disease or a selective growth advantage of tumors bearing a non-functional BRCA2.

In addition, mutations in *BRCA1/2* have been associated with advanced PCa, disease progression and worse survival; however, the effect seemed to be dependent on BRCA2 status since the contribution of *BRCA1* mutations is small if significant. PCa patients carrying BRCA1/2 mutations have significantly shorter metastasis-free survival,[55] higher Gleason score and T stage at diagnosis, and shorter time to PCa-related death[56] compared to non-carriers.

Nicotinamide adenine dinucleotide (NAD) is a fundamental molecule involved in energy production and signal transduction pathways that has been linked to proliferation, metabolism and thus, cancer development.[57] C-terminal-binding protein 1 (CtBP1) functions as a transcription repressor of tumor suppressor proteins and is tipically activated by NADH. Li *et al.* demonstrated that augmented intracellular NAD/NADH ratios are able to induce CtBP loss from the BRCA1 promoter, resulting in remarkably high BRCA1 levels.[58] Recently, Moiola *et al.* demonstrated that metabolic syndrome-like diseases and CtBP1 expression enhance prostate tumor growth. In this way, targeting CtBP1 expression might be considered as a therapeutic approach in the subset of patients with metabolic syndromes.[59]

2.2. *Tumor suppressors*

PTEN. Hyperactivation of the PI3K pathway through loss of PTEN is considered the most common PI3K aberration found in patients with PCa.[29] PTEN acts as a tumor suppressor preventing Akt activation.[60] PTEN is expressed in prostatic epithelial cells and in cells that have developed PIN. Almost 30% of localized and up to 60% of metastatic PCa exhibit PTEN mutations.[61]

Tumors display distinct metabolic programs, and altered lipid metabolism is emerging as an important mechanism in cancer progression. In this sense, Yue *et al*. reported that increased cholesteryl ester (CE) accumulation is observed in advanced PCa with PTEN loss and PI3K/AKT activation.[62] CE storage potentiated PI3K-dependent SREBP (sterol regulatory element-binding protein) activity, thereby fueling cancer aggressiveness. Notably, inhibition of cholesterol esterification considerably impaired proliferation, invasion ability and tumor growth when assessed in mouse xenograft studies.[62] Investigating lipid droplets composition, the authors were able to perform an accurate patient stratification, thus confering CE accumulation a role as a predictive marker of cancer aggressiveness compared to common histological classification methods.[62]

Co-deletion of Pten and p53 plays a fundamental role in CRPC development. This cooperation was highlighted by Wang *et al*. when using Pten/p53-deficient MEFs (mouse embryonic fibroblasts); they demonstrated that HK2 is selectively upregulated in PCa harboring this genetic deficiency.[63] To gain insights into the molecular mechanism, the authors verified that Pten deletion raises HK2 mRNA translation by AKT-mTORC1-4EBP1 pathway activation and that p53 loss positively modulates HK2 mRNA stability.[63] Supplementary studies reported that aerobic glycolysis mediated by HK2 is necessary for tumor growth in PCa murine models with Pten/p53-deficiency.[63]

Although *in vitro* studies analyzing metabolic pathways mediated by AR activation have been crucial for looking into isolated mechanisms, they cannot truly summarize the intricacy of ADT *in vivo*. Martin *et al.* worked with a PCa orthotopic Pten/p53 null model to assess metabolite production and enzymatic expression in tumors with or without androgen deprivation. AR inhibition led to a modification in glucose metabolism towards a decrease in monosaccharide levels, increased lactate and changes in Krebs cycle intermediates (a decline in citrate and a spike in fumarate and malate).[64] Furthermore, elevated mitochondrial HK2 levels and activity were reported in tumors subjected to ADT, in agreement with HK2 induction linked to increased pAKT levels.[64]

p53. p53 exerts its action largely as a transcription factor, and can trigger a variety of antiproliferative programs. In spite of the low frequency of p53 mutations in early PCa, heterozygous loss-of-function is mutated in approximately 40% of the cases in advanced PCa[65] and it is related to bone metastases. Patients with a decrease in p53 expression evidenced high stage and advanced progression of the disease;[66] in addition, low levels of this tumor suppressor were also correlated with diminished survival after prostate gland ablation.[67]

p53 is also an important regulator of metabolism. It directly activates genes such as TIGAR (a fructose biphosphatase family member that inhibits glycolysis) shunting glucose into the pentose phosphate pathway (PPP).[68] In addition, p53 activates genes, such as SCO2 (cytochrome oxidase 2 assembly protein), that enhance more efficient mitochondrial respiration, required for the accurate association of the cytochrome c oxidase (COX) complex of the electron transport chain.[69] Hence, loss of p53 tends to favor glycolysis. Furthermore, p53 was also reported to activate the expression of the liver form of glutaminase (Gls2), promoting glutamine utilization.[70]

3. Reshaping of metabolic pathways in prostate cancer

3.1. *Glycolysis and tricarboxylic acid (TCA) cycle*

Interest in cancer energetics has waxed and waned over the past 15 years. This field has now become a cornerstone of cancer biology, along with signal transduction and transcription. The accelerated aerobic glycolysis with an increase in lactate production in cancer cells has been first postulated by Warburg in 1927.[71] However, the restored concern in energetics has flourished with the proof that one of the effects of some oncogenic drivers is augmented glucose metabolism. Although aerobic glycolysis is inefficient in terms of energetic resources, the capacity to produce intermediates must be a key driver to rule metabolism in cancer cells. This characteristic yields more intermediates for anabolic processes such as the lipid, amino acid and nucleotide synthesis and the pentose-phosphate axis.[72]

The prostate gland secretes fluid that nourishes, protects and enhances

the viability of the sperm, which require androgens and AR function, key factors during reproduction.[73] Strikingly, the prostate gland is characterized by a particular metabolic role: a citrate secretor; in addition, elevated levels of this metabolite regulate sperm viability by chelating calcium, and as expected, it functions as an energy reservoir.[74] To achieve this feature, the common metabolic function of luminal epithelial cells is reshaped so that the TCA cycle does not elicit its function properly; as a result of this special condition, citrate concentrates in order to be secreted.[75] This depends upon high zinc levels within these cells and a collateral inhibition of ACO (aconitase).[76] The impaired function of the TCA cycle envisions that the normal energetic status of this gland is highly glycolytic. Although not fully explained, the metabolic pathways of greatest relevance in PCa seem to be fatty acid (FA) and glutamine metabolism.[77]

3.2. *Glutaminolysis*

A second metabolic hallmark of cancer cells is an increased glutamine uptake and utilization.[78] Hans Krebs not only characterized the TCA cycle but also conducted his research focused on glutamine utilization; he was able to denote the relevance and emphasize the role of glutamine in homeostasis. This metabolite is a conditionally essential amino acid, peculiarly under stress stimuli, in which its consumption rises markedly in certain organs such as gastrointestinal and immune systems and kidney.[79]These observations and the fact that some cancer cells die rapidly if they are deprived of glutamine, highlight the dependence of growing cancer cells on this amino acid.[80] Rapidly dividing cells employ glutamine for ATP production and as a carbon and nitrogen reservoir in order to generate vast biomass.[81] The advantages of the glutaminolytic pathway in cancer cells consist of the citric acid entrance via 2-oxoglutarate, which primes lipid biosynthesis (acetyl-CoA) or non-essential amino acids synthesis.[82]

Glutamine enters the cells via specific transporters and is further catabolized by mitochondrial glutaminases to the products glutamate and ammonium.[83] The expression of enzymes that take part in the glutaminolytic pathway fluctuate in cancer; however, in most of the cases the altered expression is able to rewire glutamine metabolism in order to cope with energy demands and carbon and nitrogen generation. GLS1 is broadly expressed in normal tissue and is believed to have a critical role in many cancers, whereas glutaminase 2 (GLS2) expression is restricted to the liver, brain, pituitary gland and pancreas.[84]

The nitrogen from glutamine supports the supply of many amino acid pools through the function of aminotransferases.[85] The effective production of proline can be achieved from the nitrogen and carbon obtained from glutamate, other than the reaction steps involved in transamination; this amino acid has a crucial participation in the production of collagen.[86] Enzyme expression with a role in the synthesis and degradation of proline can be altered by MYC oncoprotein, tilting the balance towards an increase of this amino acid from the glutamate obtained from glutamine.[87] Glutamine can also participate in nucleotide biosynthesis since aspartate derived from glutamine serves as a fundamental carbon reservoir for pyrimidine and purine rings via the Krebs cycle and transamination reactions.[88]

In a recent work, Wang *et al.* proved that ASCT2 (a glutamine transporter) is vastly expressed in PCa patient samples.[89] In a second instance, this work provided insights into the molecular mechanism affected by the specific transporter. By using chemical or shRNA tools to inhibit ASCT2 function, these authors explained a reduction in glutamine uptake, cell cycle progression, cell growth and mTORC1 pathway activation in different cell lines.[89] On a metabolic side, chemical inhibition decreased basal OCR; ASCT2 shRNA knockdown conducted in PC-3 cell xenografts significantly impaired tumor growth and metastasis *in vivo*.[89] Therefore, ASCT2 is considered a putative therapeutic target in PCa.

3.3. *Lipid metabolism*

In order to boost the efficient conversion of glucose into the macromolecules and intermediates needed, cancer cells rewire their metabolism and thus, shift to aerobic glycolysis with lactate production, paired with augmented glucose uptake. Although the reason why cancer cells undergo this Warburg effect is still uncertain, several authors hypothesize that glutamine and glucose metabolism may be linked to acetyl-CoA and NADPH production, both molecules considered essential for the synthesis of fatty acids (FAs).[90] Lipid metabolism is an essential cellular process that converts nutrients into metabolic intermediates for membrane biosynthesis, energy storage and the generation of signaling molecules.[90] Membrane lipids also give rise to second messengers, such as PtdIns(3,4,5)P3, which are formed in response to extracellular stimuli.[90]

After Warburg's pioneer work, Medes *et al*. observed that tumors convert glucose or acetate into lipids at a rate similar to that observed in liver.[91] However, this study concluded that the process is probably too slow to supply the lipid needs of a rapidly growing tumor. On the other hand, another study demonstrated that tumor cells produce almost all their FAs through *de novo* synthesis.[92] Nonetheless, decades later, FASN overexpression and hyperactivity was associated with malignant cells. Several studies have since confirmed the relevance of FAs biosynthesis for cancer cell growth and survival and the diverse aspects of this pathway that promotes tumorigenesis and tumor progression.[93]

Induction of epithelial-mesenchymal transition (EMT) by transforming growth factor β (TGFβ) in PCa cells induces the expression of cyclooxygenase 2 (COX2), which enhances cell migration via prostaglandin E2 (PGE2) signaling.[94] The induction of EMT requires complex remodeling of cellular lipid composition to favor changes in membrane fluidity required for cell migration.

Metastatic dissemination also depends on the induction of angiogenesis.[95] Signaling lipids have important roles in inducing vessel growth and recruiting immune cells, which promote tumor angiogenesis.[96] Endothelial cells utilize FAs degradation not for energy generation, but to produce substrates for nucleotide biosynthesis.[97] Moreover, uptake of exogenous FAs by PCa cells favors the expression of vascular endothelial growth factor (VEGF) through a system that depends upon FA binding protein 5 (FABP5) and peroxisome proliferator-activated receptor gamma (PPARγ).[98] FAs in the tumor micro-environment activate pro-angiogenic signaling and facilitate proliferation of endothelial cells to provide cancer cells with a growth advantage.

Besides the metabolome alterations found in PCa, the expression of specific lipidomes could play a crucial role in the progression of this disease. Burch and colleagues identified distinct lipid subclasses such as phosphatidylcholines (Pcs), phosphatidylethanolamines (PEs), glycerophosphoinositols (PIs) that are upregulated in PCa.[99] Molecular analysis of fundamental enzymes that play a role in lipid metabolism highlighted the upregulation of choline kinase alpha in the metastatic cells.[99] Therefore, the lipidome characterization could provide markers that are exclusively of aggressive PCa.

3.4. Pentose phosphate pathway

There has been a resurgence of interest in understanding the role of the pentose phosphate pathway in cancer. This axis confers an advantage for enhanced cell growth since it yields nucleotide intermediates and favors the regeneration of the reducing agent NADPH, a key player in ROS (reactive oxygen species) scavenging. Several years ago, Zampella *et al.,* suggested that G6PD (glucose-6-phosphate dehydrogenase), the rate-limiting enzyme of this axis, was a possible clinical indicator of PCa[100] and was further confirmed its correlation with Gleason score[101].

Due to the renewed interest in the role of the PPP in the generation of the metabolic precursors and reducing agents, Tsouko *et al.* demonstrated that glucose-6-phosphate dehydrogenase (G6PD) expression was elevated with androgen treatment in androgen sensitive PCa cell lines.[102] This upregulation was disrupted upon rapamycin treatment, suggesting a key role of mTOR (mammalian target of rapamycin) for the augmented flux through this pathway.[102] Remarkably, G6PD mRNA and protein levels were not correlated, typical of transcriptional and post-transcriptional regulation. As it was expected, mTOR could also regulate G6PD expression at a post-transcriptional level.[102]

Of note, the inhibition of G6PD with dehydroepiandrosterone (DHEA) led to a 40% decrease of NADPH/NADP+ ratio, which has been hypothesized to adjust cellular hydroperoxide metabolism.[103] In line with this, Li *et al.* used a pharmacological combination of DHEA with a well known glycolytic inhibitor, 2-deoxyglucose (2-DG). These authors demonstrated that human PCa cells under the combination treatment display a reduction in cell survival with additive cytotoxicity, associated with alterations in glutathione (GSH) metabolism.[104] As a consequence, inhibiting the PPP could selectively

target cancer cells causing a metabolic oxidative stress, by which the cells would be unable to overcome detoxification of high intracellular levels of ROS.[104]

By using siRNA-mediated gene silencing of more than 200 metabolic enzymes on metastatic PCa cell lines, Ros and colleagues identified 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 4 (PFKFB4) as a key player for the survival of PCa cells.[105] PFKFB4 shunts glucose into the PPP and inhibiting this enzyme induces ROS production and cell death, denoting that PFKFB4 could be exploited for therapeutic gain.[105]

4. Concluding remarks

Metabolic changes are a well-defined hallmark of cancer and represent the outcome to alterations in the activity of diverse oncogenes and tumor suppressors. A broaden energetic repertoire supports the reprogramming of glucose, lipid, hormone and amino acid metabolic pathways during malignant transformation and tumor development in both the prostate gland in particular and other cancer cells in general.

The metabolic phenotype of PCa cells is supported by mutations and external responses to the tumor microenvironment. Signaling pathways controlling sustained growth and survival are usually activated by the loss of tumor suppressors or the activation of oncoproteins. The modified signaling contributes to changes in cellular metabolism that support the requirements of cell division. Anomalous microenvironmental status such as hypoxia or low pH triggers cellular responses, which modify metabolic activity in order to provide sufficient ATP levels, biosynthetic intermediates and a balanced redox status. Particularly, metabolic pathways significantly altered in PCa are glutaminolysis and lipid metabolism. Of note, basal metabolic status in luminal epithelial cells of the prostate gland differs from other tissues since TCA is altered due to the need for high citrate supply giving rise to a more glycolytic phenotype.

PCa is characterized as a heterogeneous disease due to the complexity of its biological, hormonal and molecular features. Clinical heterogeneity makes the situation even more difficult as response to particular therapies is markedly variable. Thus, significant clinical challenge emerges to target the diverse phenotypes intra and inter-tumorally. **Figure 1** provides a schematic representation of the main deregulated metabolic pathways in PCa and the tumor suppressors and oncoproteins involved. Future directions to target CRPC should be focused not only on the growth and survival capability of tumor cells, but also on these metabolic pathways that support malignant growth. Taking into account these alterations and targeting them, can be exploited for therapeutic gain. Understanding tumor metabolism in the context of oncogenic and suppressor signals as well as the role of the tumor microenvironment, will drive the development of targeted personalized therapies.

Figure legend

Figure 1. The regulation of metabolic pathways in prostate cancer. Oncoproteins and tumor suppressors are closely linked to metabolic pathways through transcriptional, post-transcriptional or epigenetic regulation of metabolic enzymes. Cancer cells exploit signaling and metabolic pathways to support uncontrolled growth providing numerous intermediates for biosynthesis. Brackets depict the main metabolic pathways altered in PCa. Purple circles: tumor suppresors; orange circles: oncoproteins. ACO: Aconitase; GLS: Glutaminase; PTEN: Phosphatase and tensin homologue; PI3K: Phosphatidylinositol 3-kinase; HK2: Hexokinase 2; FASN: Fatty acid synthase; ACACA: Acetyl-CoA carboxylase Alpha; G6PD: Glucose 6-phosphate dehydrogenase; AR: Androgen receptor.

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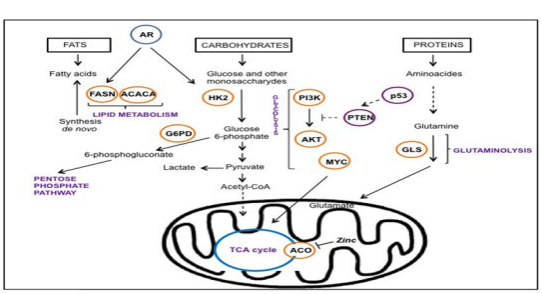
Conflict of interest

The authors declare no conflict of interest.



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