Targeting the 5′-AMP-activated protein kinase and related metabolic pathways for the treatment of prostate cancer

Petra Popovicsabc, Daniel E Frigo de, Andrew V Schallyafg & Ferenc G Rick MD PhDah

a 1Veterans Affairs Medical Center and South Florida Veterans Affairs Foundation for Research and Education, Research (151) 2A127, 1201 NW 16th St, Miami, FL 33125, USA +1 305 5753477; +1 305 5753126;
b 2University of Miami, Miller School of Medicine, Division of Cardiovascular Diseases, Department of Medicine, Miami, FL 33136, USA
c 3Department of Medicine III, Medical Faculty Carl Gustav Carus, D-01307 TU Dresden, Germany
d 4University of Houston, Center for Nuclear Receptors and Cell Signaling, Department of Biology and Biochemistry, Houston, TX 77204, USA
e 5Houston Methodist Research Institute, Genomic Medicine Program, Houston, TX 77030, USA
f 6University of Miami, Miller School of Medicine, Division of Hematology/Oncology, Department of Medicine, Miami, FL 33136, USA
g 7University of Miami, Miller School of Medicine, Division of Endocrinology, Department of Medicine, Miami, FL 33136, USA
h 8Florida International University, Herbert Wertheim College of Medicine, Department of Urology, Miami, FL 33199, USA

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Targeting the 5′-AMP-activated protein kinase and related metabolic pathways for the treatment of prostate cancer

Petra Popovics, Daniel E Frigo, Andrew V Schally & Ferenc G Rick†
†Veterans Affairs Medical Center and South Florida Veterans Affairs Foundation for Research and Education, Miami, FL, USA

Introduction: Increasing evidence suggests that prostate cancer cells undergo unique metabolic reprogramming during transformation. A master regulator of cellular homeostasis, 5′-AMP-activated protein kinase (AMPK), directs metabolic adaptation that supports the growth demands of rapidly dividing cancer cells. The utilization of AMPK as a therapeutic target may therefore provide an effective strategy in the treatment of prostate cancer.

Areas covered: Our review describes the regulation of AMPK by androgens and upstream kinases including the calcium/calmodulin-dependent protein kinase kinase 2 (CaMKK2) in prostate cancer. Oncogenic, AMPK-regulated pathways that direct various metabolic processes are also addressed. Furthermore, we discuss the role of AMPK in growth arrest and autophagy as a potential survival pathway for cancer cells. In addition, by regulating non-metabolic pathways, AMPK may stimulate migration and mitosis. Finally, this review summarizes efforts to treat prostate cancer with pharmacological agents capable of modulating AMPK signaling.

Expert opinion: Current research is primarily focused on developing drugs that activate AMPK as a treatment for prostate cancer. However, oncogenic aspects of AMPK signaling calls for caution about employing such therapies. We think that inhibitors of CaMKK2 or AMPK, or perhaps the modulation of downstream targets of AMPK, will gain importance in the clinical management of prostate cancer.

Keywords: 5′-AMP-activated protein kinase, calcium/calmodulin-dependent protein kinase kinase 2, cancer metabolism, prostate cancer


1. Introduction

Prostate cancer is the most frequent noncutaneous malignancy in men, accounting for 27% of newly diagnosed cases and 10% of all cancer-related deaths in the US in 2014 [1]. The median survival of patients with castration-resistant prostate cancer (CRPC) is estimated to be < 2 years [2]. In recent years, several promising chemotherapeutic agents have been approved by the FDA for the treatment of CRPC. However, these new agents only extend life expectancy for a few months [3,4]. Consequently, the search for more effective drugs in the management of prostate cancer is still in progress.

The unregulated, rapid proliferation seen in tumors demands substantial changes in cellular metabolism. The first evidence on the adaptation of metabolic homeostasis in cancer cells was provided in the 1920s by Otto Warburg. He demonstrated an increased rate of glycolysis and lactate secretion even when sufficient oxygen was available (aerobic glycolysis) [5]. This so-called Warburg-effect was paradoxical at
Article highlights.

- 5'-AMP-activated protein kinase (AMPK) controls the metabolic adaptation of prostate cancer cells.
- AMPK activity is stimulated by androgen receptor signaling via calcium/calmodulin-dependent protein kinase 2.
- AMPK supports prostate cancer growth by regulating glycolysis, lipogenesis, oxidative phosphorylation and protein metabolism.
- Tumor survival strategies of starvation-induced growth arrest and autophagy are also promoted by AMPK.
- Development of pharmacological strategies that block AMPK signaling is clearly needed for the treatment of prostate malignancies.

This box summarizes key points contained in the article.

the time largely because it was difficult to rationalize why cancer cells would prefer glycolysis over mitochondrial oxidative phosphorylation – a metabolic pathway that is much more efficient in generating ATP (2 mol ATP with aerobic glycolysis vs 31 mol with oxidative phosphorylation). Warburg believed that the effect was due to a failure in mitochondrial oxidative phosphorylation, although this hypothesis was subsequently disproved [6]. It is now generally accepted that increased glycolysis is required to generate intermediates as building blocks for biosynthetic pathways that are essential for the rapidly dividing cancer cells [7,8]. Most of the pyruvate that enters the tricarboxylic acid (TCA) cycle, rather than being converted into lactate, is utilized for biosynthetic pathways [9]. The export of citrate from the mitochondria to the cytosol for lipid synthesis is a hallmark of tumor cells which results from a truncated TCA cycle. However, other intermediates of the cycle also provide substrates for protein and nucleotide synthesis [10,11]. In addition, glutamine uptake is facilitated in cancer cells, providing metabolites and energy to the rapidly dividing cells by generating intermediates of the TCA cycle in a process termed ‘anaplerosis’ [12].

In contrast to most cancers, metabolic reprogramming in prostate cancer is fairly distinct. First, nonmalignant prostatic epithelial cells possess a unique capability to accumulate high levels of intramitochondrial zinc. This in turn inhibits the activity of mitochondrial aconitase, the enzyme that catalyses the conversion of citrate to D-isocitrate. This inhibition leads to a truncated TCA cycle. The surplus citrate is then transported to the cytosol and secreted into the prostatic fluid [13,14]. On the malignant transformation of prostate cells, intracellular zinc levels drop ~66% in part due to the down-regulation of zinc transporters [14,15]. This leads to the recovery of the functional TCA cycle and increased ATP production that can provide energy for accelerated proliferation [14]. This ‘TCA cycle release’ presumably also helps replenish downstream intermediates that can again be siphoned off for more biosynthetic reactions. Accordingly, this altered metabolism appears to be a key step in tumoral transformation, since the intracellular concentration of zinc is inversely correlated with the aggressiveness of prostate cancer [16].

Consequently, in prostate cancer cells, citrate oxidation and oxidative phosphorylation are increased, whereas aerobic glycolysis may have a less significant role [17,18]. This is further supported by the clinical observation that positron emission tomography (PET) imaging of 18F-fluorodeoxyglucose uptake, a marker of glycolysis, is only a modest indicator of prostate cancer [19]. In contrast, PET imaging analogs of fatty acids and acetate that report on elevated TCA cycle activity and lipid metabolism may be more sensitive prostate cancer detection agents [20-22].

In recent years, there have been increasing efforts to identify the key molecular drivers of metabolic reprogramming in prostate cancer. 5'-AMP-activated protein kinase (AMPK) is a master regulator of energy homeostasis in normal cells. Therefore, it has been suspected to play an important role in metabolic reprogramming during malignant transformation. Our review: i) focuses on the specific role of this molecule in prostate cancer, a malignancy that is metabolically distinct from other cancers; and ii) provides a mechanistic overview of pharmacological strategies currently being used to manipulate AMPK activity.

2. Role of AMPK in prostate cancer metabolism

2.1 Regulation of AMPK in prostate cancer
AMPK is best known as a sensor of cellular energy levels. In this regard, AMP/ADP binding to the γ subunit allosterically activates AMPK, whereas ATP binding inhibits the kinase complex [23]. Although AMPK is classically activated by conditions that elicit cellular stress, such as under conditions of hypoxia or glucose deprivation, it can be more directly regulated through post-translational modifications. Chief among these modifications is the phosphorylation of threonine-172 on AMPK’s α-catalytic subunit. This residue is located on the activation loop of AMPKα and its phosphorylation is required for full AMPK activation [23]. There are three reported upstream AMPK kinases: liver kinase B1 (LKB1), calcium/calmodulin-dependent protein kinase kinase 2 (CaMKK2, also known as CaMKKβ) and TGF-β activated kinase-1 (TAK1) [24]. The dominant AMPK kinase in the body is thought to be LKB1, a kinase that has been demonstrated to be a tumor suppressor in several tissues [25]. However, several lines of evidence suggest that LKB1 is not a major regulator of AMPK in the prostate. First, although LKB1 has been implicated as a tumor suppressor in a number of different cancer types, prostate cancer is not one of them [26]. This was supported by an animal study that demonstrated that the genetic deletion of LKB1 increased the incidence of different tumor types in PTEN+/− mice, with the exception of prostate cancer, which was not altered [27]. Second, androgens were reported to decrease LKB1 mRNA levels.
and subsequent AMPK phosphorylation in mouse 3T3-L1 cells [28]. This effect on AMPK is contrary to the marked increase in AMPK phosphorylation observed in androgen-treated prostate cancer cells [29]. Third, LKB1 is not highly expressed in many prostate cell models nor is it regulated by androgen receptor (AR) (unpublished data). Fourth, in a study that suggested conditional 

Lkb1 deficiency in mice caused prostatic neoplasia, the authors: i) deleted Lkb1 using a mainly gastrointestinal track-specific Cre and not a prostate-specific driven Cre and, importantly; and ii) observed continued high levels of phosphorylated/activated AMPK in the Lkb1-deficient prostate [30]. This led the authors to conclude that LKB1 does not regulate AMPK in the prostate and therefore some other upstream kinase is likely responsible. If LKB1 does regulate prostate growth, it may be through the phosphorylation and stabilization of PTEN [31,32] - one of the most commonly mutated genes in prostate cancer [33].

TAK1 may also phosphorylate and activate AMPK. However, the context(s) in which this occurs in vivo and whether this requires LKB1 requires further investigation [34,35]. The gene for TAK1, MAP3K7, is located in a chromosomal region that is frequently lost during the development of prostate cancer. Despite early research suggesting that MAP3K7 does not correlate with loss of heterozygosity status and hence is not a target gene in prostate cancer [36], more recent evidence strongly suggests that the deletion of MAP3K7 correlates with advanced tumor stage, Gleason score, lymph node metastasis and early biochemical recurrence [37,38]. If AMPK was a downstream target of TAK1 in the prostate, these data would be in direct contrast to the recent findings that phosphorylated/activated AMPK levels are elevated in prostate cancer patient samples relative to normal prostate and, importantly, further elevated in advanced, recurrent prostate cancer [39,40]. Additionally, while functional data confirmed TAK1’s role as a tumor suppressor in prostate tumorigenesis, the known stress kinases p38 and c-Jun N-terminal kinase were implicated as the downstream effectors [41]. Taken together, these data indicate that TAK1 is likely not the upstream AMPK kinase in the prostate.

Recently, AMPK was identified as a substrate of CaMKK2 [42-44]. Work from our laboratory has demonstrated that androgens, in an AR-dependent manner, increase prostate cancer cellular migration and invasion through the direct expression of CaMKK2 and subsequent phosphorylation/activation of AMPK [29]. Later, two independent groups confirmed our findings in vitro as well as in multiple clinical cohorts [45,46]. In patients, CaMKK2 levels track with disease progression and are highest in CRPC [45]. Accordingly, CaMKK2 levels also correlate with Gleason score [46]. Importantly, the AR-binding site, which we demonstrated was responsible for AR-mediated CaMKK2 expression [29], is one of the most robust AR-binding sites in CRPC tissues [47], thus indicating AR activates this signaling cascade in the advanced disease. Correspondingly, it was recently demonstrated that levels of the threonine-172 phosphorylated form of AMPK, a direct target of CaMKK2, are increased in clinical prostate cancer samples and highest in recurrent prostate cancers [39]. In addition, the levels of the serine-79 phosphorylated form of acetyl-CoA carboxylase (ACC), a direct target of AMPK, are increased in clinical prostate cancer samples [40]. More recently, the tumor suppressive microRNA, miR-224, was shown to exert antiproliferative effects in prostate cancer cells through the direct downregulation of CaMKK2 [48]. Furthermore, combined low miR-224 and high CaMKK2 expression correlated in patients with advanced clinical stage and shortened overall survival. Interestingly, in this study CaMKK2 was demonstrated to have a proliferative role in AR-negative DU145 prostate cancer cells, indicating that in highly aggressive prostate cancers CaMKK2 may be expressed independently of AR. Collectively, these studies suggest that CaMKK2 is the dominant upstream AMPK kinase in the prostate (Figure 1). However, as this is a nascent area of research, further studies are needed to validate CaMKK2 as a bona fide new therapeutic target.

Additional post-translational modifications of AMPK have been reported. These include myristoylation and serine-108 phosphorylation of the β subunit [49-51]. Serine-108 appears to be a site for autophosphorylation [50,51]. It is unknown at this time if this site can also be targeted by other kinases. While both of these modifications appear necessary for full allosteric activation of AMPK by AMP, it is not clear if they are required in prostate cancer where CaMKK2-mediated phosphorylation of threonine-172 appears sufficient to increase AMPK activity [29]. Interestingly, under certain pharmacologically induced conditions, AMPK may be activated in the absence of phosphorylation at both threonine-172 of the α subunit and serine-108 of the β subunit [51]. However, whether this ever occurs from the result of endogenous signaling remains to be seen.

2.2 Downstream targets of AMPK

AMPK’s role as a master regulator of metabolism has largely been defined in basic physiological processes. Here, AMPK facilitates the management of various cellular stresses and conservation of energy in part by activating catabolic processes and blocking anabolic processes. Many of these actions are consistent with a potential role of AMPK as a tumor suppressor. For example, in p53 wild-type cells, increased AMPK activity can lead to the phosphorylation of p53 on serine-15 [52]. This results in increased p53 activity concomitant with increased p21 levels and a G1/S cell-cycle arrest. However, whereas persistent AMPK activation augmented p53-dependent cellular senescence, limited AMPK activation promoted cell survival under conditions of glucose deprivation, suggesting that in some contexts more controlled AMPK signaling could function in an oncogenic role (Figure 2) [52]. Likewise, increased AMPK signaling could also lead to the phosphorylation and stabilization of the cell cycle inhibitor p27, a signaling event that enabled survival during growth factor withdrawal and/or metabolic stress through the induction of...
Figure 1. AMPK-regulated metabolic pathways that may play key roles in the pathogenesis of prostate cancer are shown. DHT mediates the ability of AR to initiate the transcription of various genes, including CaMKK2, the predominant upstream regulatory kinase of AMPK in the prostate. AMPK is also stimulated by stress and starvation through elevated AMP/ADP levels or by other unknown pathways. AMPK affects several aspects of cellular metabolism. AMPK may increase glycolytic flux by stimulating the glycolytic enzymes (PFKFB-2 and -3), inhibiting the hexosamine biosynthetic pathway (via GFAT1), or by increasing the membrane levels of glucose transporters (GLUT1 and GLUT4). Enzymes of lipid metabolism, namely ACC1, ACC2 and HMGCR, are inhibited by AMPK signaling. This effect in turn may lead to increased levels of NADPH that fuels anabolic reactions and redox homeostasis in cancer cells. Phosphorylation of the transcription factors SREBP-1 and HNF-4α potentiates the expression of lipogenic enzymes. AMPK may also stimulate lipid oxidation by the direct activation of histone H2B. AMPK facilitates oxidative phosphorylation by the direct or indirect (via SIRT1) phosphorylation of PGC-1α. PGC-1α regulates the transcription of various mitochondrial and lipogenic genes. Protein metabolism may also be affected by prostatic AMPK signaling; AMPK stimulates the activity of PRODH, a key enzyme of proline metabolism, thereby facilitating the pentose phosphate pathway.

ACC1: Acetyl-CoA carboxylase 1; ACC2: Acetyl-CoA carboxylase 2; AMPK: 5'-AMP-activated protein kinase; AR: Androgen receptor; CaMKK2: Calcium/calmodulin-dependent protein kinase kinase 2; CPT1C: Carnitine palmitoyltransferase 1-C; DHT: Dihydrotestosterone; FASN: Fatty acid synthase; FDPs: Farnesyldiphosphate synthase; GFAT1: Glutamine:fructose-6-phosphate amidotransferase 1; GLUT: Glucose transporter; HMGCR: 3-hydroxy-3-methyl-glutaryl-CoA; HNF-4α: Hepatocyte nuclear factor-4α; PFKFB: 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase; PGCG-1α: Peroxisome-proliferator-activated receptor γ coactivator 1α; PRODH: Proline dehydrogenase; SCAP: SREBP cleavage-activating protein; SIRT1: Sirtuin 1; SREBP-1: Sterol regulatory element binding proteins-1.
Figure 2. AMPK promotes prostate cancer cell survival by commencing autophagy and growth arrest during starvation. AMPK triggers the activation of FOXO3 and other potential transcription factors leading to growth arrest and autophagy, increasing resistance to stress. AMPK facilitates survival under nutrient deprivation by initiating G1/S cell-cycle arrest (through the p53/p21 pathway) and decreasing translation (via phosphorylating eEF2K). AMPK promotes autophagy by: i) inhibiting the negative regulator of autophagy, the mTOR complex; ii) inhibiting the non-autophagy complex VPS34/Beclin-1; iii) stimulating the autophagy complex Atg14L/VPS34/Beclin-1; and iv) activating ULK1 and ULK2. In addition, AMPK blocks the inhibitory action of IRS1/PI3K/Akt signaling on TSC1/2, consequently suppressing the stimulation of Rheb on the mTOR complex. AMPK-induced autophagy facilitates metabolic adaptation and provides nutrients for cancer cells.

AMPK: 5'-AMP-activated protein kinase; Atg: Autophagy-related protein; DEPTOR: DEP domain-containing mTOR-interacting protein; eEF2: Eukaryotic elongation factor 2; eEF2K: Eukaryotic elongation factor 2 kinase; IRS-1: Insulin receptor substrate-1; mTOR: Mammalian target of rapamycin; P38: Phosphoinositide 3-kinase; Pras40: Proline-rich Akt substrate 1; raptor: Regulatory-associated protein of mTOR; Rheb: Ras homolog enriched in brain.
ampk proteins that control GLUT4-containing vesicle trafficking. AMPK can then promote glycolysis by dually phosphorylation and inhibition of eEF2 (Figure 1), an essential factor for protein synthesis. This adaptation conferred resistance to nutrient deprivation, a common element of the tumor microenvironment.

AMPK can more directly alter cancer metabolism through phosphorylation of the bifunctional enzyme 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 2-phosphatase (PFKFB), a rate-limiting step of glycolysis (Figure 1) [55-57]. Specifically, AMPK can phosphorylate two isoforms of PFKFB: PFKFB2 and PFKFB3. AMPK-mediated phosphorylation of these isoforms increases their kinase activity and hence increases flux through glycolysis. In prostate cancer, there is an additional level of regulation as androgens can stimulate the expression of PFKFB2 [58]. This is further complicated by the tumor microenvironment, where low pH conditions induce AMPK activation. AMPK can then promote glycolysis by dually increasing PFKFB3 protein levels and serine residue phosphorylation [59]. Although AR-AMPK-PFKFB signaling is suspected to occur in prostate cancer [45], the exact isoforms regulated by AMPK and/or AR, how they are regulated and their functional significance are still incompletely defined. Furthermore, whether AMPK-mediated glycolytic flux is amplified by the previously described phosphorylation and inhibition of glutamine:fructose-6-phosphate amidotransferase 1, the rate-limiting enzyme of the hexosamine biosynthetic pathway, is not known [60].

In addition to increased glycolysis, AMPK may also promote more general glucose uptake (Figure 1). Although it has yet to be demonstrated in prostate cancer, it is possible that regulatory mechanisms demonstrated in other tissues may have relevance in the prostate. For example, in muscle and fat, AMPK promotes glucose transporter (GLUT) 4 translocation to the plasma membrane and subsequent glucose uptake [61]. This occurs through the AMPK-mediated phosphorylation/regulation of TBC1D1 and TBC1D4/AS160, proteins that control GLUT4-containing vesicle trafficking. Furthermore, AMPK has previously been shown to increase GLUT1 levels via multiple mechanisms [62-64]. Thus, AMPK may regulate these or other related glucose transporters in prostate cancer through similar means.

One of the oldest known functions of AMPK is its ability to regulate lipid metabolism (Figure 1) [65]. This includes the phosphorylation and subsequent inhibition or downregulation of several known targets including ACC1, ACC2, 3-hydroxy-3-methyl-glutaryl-CoA (HMGCR) and the lipogenic transcription factors sterol regulatory element binding proteins-1 and -2 (SREBP-1 and -2) and hepatocyte nuclear factor-4α (HNF-4α) [66-69]. Recent evidence suggests that AMPK-mediated inhibition of ACC1 and ACC2 may promote cancer [70]. Under conditions of glucose deprivation or matrix detachment, AMPK can phosphorylate and inhibit ACC2 and ACC1, respectively. This results in the maintenance of pro-tumor NADPH levels (used for various tumor anabolic reactions and redox homeostasis) through distinct mechanisms. However, despite all of the previous observations, it is unclear whether AMPK signaling through any of these downstream targets (ACC1, ACC2, HMGCR, SREBP-1, SREBP-2, HNF-4α) will impact prostate cancer. This is because these signaling events may be overridden by AR signaling (Figure 1). One of the common traits of prostate cancer is an increase in lipogenesis [71]. AR signaling increases the expression of several key lipogenic genes such as fatty acid synthase, ATP-citrate lyase, HMGCR, ACC and farnesyl diposphosphate synthase through the increased expression of the SREBPs and SREBP cleavage-activating protein, which further potentiates SREBP activity [71,72]. Hence, AMPK’s inhibitory effects on lipogenesis may be negated by dominant pro-lipogenic AR signaling.

Paradoxically, despite the elevated intracellular lipid levels often observed in tumors, prostate cancers also demonstrate increased fatty acid and glucose oxidation/flux through the TCA cycle [18,73,74]. This is due in part to decreased zinc levels. Decreased zinc levels relieve acotinase repression, allowing a greater proportion of substrates to continue through the TCA cycle [17,18]. AMPK can also promote this process through the induction of peroxisome-proliferator-activated receptor γ coactivator 1α (PGC-1α), a master regulator of mitochondrial biogenesis (Figure 1) [75]. However, it should be noted that increased PGC-1α expression has also been linked to augmented lipogenesis in liver and colon cancers [76]. Interestingly, AMPK may also indirectly activate PGC-1α through the phosphorylation/activation of sirtuin 1 (SIRT1) [77]. SIRT1 can then increase PGC-1α activity through deacetylation. In prostate cancer, AR signaling increases PGC-1α-mediated mitochondrial biogenesis via AMPK [39]. Correspondingly, knockdown of AMPK or PGC-1α impaired AR-mediated cancer cell growth. Whether this AR-AMPK-PGC-1α signaling cascade plays additional roles in prostate cancer metabolism is unknown. It also remains to be seen if AMPK can increase fatty acid oxidation through other mechanisms such as the above-described targeting of ACC2 [78] and/or the histone H2B-mediated transcriptional regulation of carnitine palmitoyltransferase 1-C (CPT1C) [78], a CPT1 (rate-limiting step in β-oxidation) variant that is frequently upregulated in lung tumors and increases tumorigenic fatty acid oxidation and subsequent drug resistance [79].

Although AMPK’s effects on sugar and lipid metabolism are well described, less is known about its effects on amino
acid metabolism. The first enzyme in proline metabolism is proline dehydrogenase (oxidase, PRODH/POX). Although PRODH was initially identified as a metabolic tumor suppressor [80,81], more recent findings demonstrate that in the tumor microenvironment, AMPK combats stress and promotes colon cancer cell survival through the enhancement of PRODH activity [82]. Interestingly, this resulted in increased flux through the pentose phosphate pathway, a process we recently demonstrated to be: i) stimulated by AR-mammalian target of rapamycin (mTOR) signaling; and ii) required for prostate cancer progression [83]. Correspondingly, mining of existing genomic data reveals that elevated PRODH levels predicted poor prognosis in prostate cancer patients [84]. However, it is still unclear how AMPK regulates PRODH activity and whether this occurs in prostate cancer.

Autophagy is an AMPK-regulated cellular process that involves the lysosomal-mediated turnover of subcellular macromolecules and organelles. Although initial studies suggested autophagy as a tumor suppressor process, recent data have indicated a more complicated role for autophagy in cancer (similar to AMPK), whereby autophagy may initially function as a tumor suppressor but later promote disease progression and therapy resistance (Figure 2) [85]. Indeed, AMPK-mediated autophagy has been implicated in prostate cancer progression [86,87]. However, there is disagreement regarding whether AR signaling activates or blocks autophagy [86-89]. This is particularly surprising given the robust, direct activation of AMPK by AR-mediated CaMKK2 expression [29,39,45-47]. The discrepancy may be due to the treatment duration (e.g., transient vs sustained), use of nonselective AMPK and autophagy small molecule modulators (e.g., 5-aminoimidazole-4-carboxamide 1-b-D-ribofuranoside [AICAR], metformin, chloroquine, etc.) and treatment conditions (e.g., hypoxia, use of charcoal-stripped serum to create an 'androgen-deprived' environment [note, charcoal-stripping also removes numerous other steroid and peptide hormones/growth factors that could impact autophagy]). To the last point, switching of AR-negative PC-3 prostate cancer cells to charcoal-stripped serum-containing media activates AMPK and autophagy, indicating this 'androgen-deprivation' approach impacts AMPK signaling and autophagy in an AR-independent manner (unpublished data).

AMPK can promote autophagy through both direct and indirect mechanisms (Figure 2). The core autophagy components ULK1 and possibly ULK2 can directly be phosphorylated and activated by AMPK [90]. In addition, AMPK has more recently been shown to regulate VPS34 complexes through the direct phosphorylation of VPS34 itself and Beclin-1 [91]. AMPK is also well known to indirectly promote autophagy through the inhibition of mTOR signaling, an antagonist of autophagy [90]. This occurs mainly through...
two mechanisms. First, AMPK can directly phosphorylate TSC2 and potentiate its repressive effects on the mTORC1 complex [92]. Second, AMPK can also directly phosphorylate the mTOR binding partner raptor [93]. This phosphorylation event induces 14–3–3 binding to raptor, resulting in inhibition of the mTORC1-signaling complex. Furthermore, it is also possible that AMPK may regulate mTOR through targeting upstream components of the phosphoinositide 3-kinase (PI3K)/Akt signaling cascade such as insulin receptor substrate-1 [94]. However, this is complicated by the fact that most advanced prostate cancers demonstrate elevated PI3K/Akt signaling and hence, could be resistant to this type of regulation [84]. Moreover, predicting AMPK-mediated mTOR effects may be difficult given the unusual crosstalk that occurs in prostate cancer.

Counter to the common dogma that AMPK and mTOR signaling mutually oppose one another, in prostate cancer these two signaling cascades can simultaneously occur [29,39,83,95]. In this regard, prostate cancers may be unique. Because of this, caution should be used when extrapolating results from studies in other cancers/tissues to the prostate. Whereas this paradox may seem counterintuitive, emerging data are beginning to mechanistically explain how this occurs. Correspondingly, in prostate cancer, AR signaling increases the expression of a splice variant of TSC2, termed ‘TSC2A’, that cannot block mTOR signaling [96]. This has the net effect of increasing prostate cancer cell growth possibly by allowing the cancer cell to enjoy the pro-tumorigenic aspects of both signaling cascades.

3. Nonmetabolic roles of AMPK

While the majority of research on AMPK focuses on its role as a master regulator of metabolism, it is important to note that nonmetabolic functions of AMPK have recently been described that may also significantly influence AMPK’s role in prostate cancer (Figure 3). To that end, AMPK promoted prostate cancer cell migration and invasion [29], an effect that may be mediated through the phosphorylation of the microtubule plus end protein CLIP-170 [97]. Several groups have suggested that AMPK may also have an active role in mitosis [98-101]. In these studies, AMPK was required for the proper completion of mitosis through targeting components of the mitotic spindle assembly, controlling the breakdown and reassembly of the Golgi apparatus and regulating cytoskeletal structure. Although this might appear at odds with the above-described effects of AMPK on p53, p21 and p27, these could collectively be viewed as a protective mechanism for the cell, making sure it does not prematurely progress through the cell cycle. This would be in contrast to a more classical oncogenic role for AMPK [102]. In this study, AMPK was an essential downstream effector of either oncogenic HRasV12 or Pten deletion. Under these conditions, AMPK appears to phosphorylate and inhibit the tumor suppressor retinoblastoma (Rb). Conversely, in skin AMPK can phosphorylate the canonical oncogene BRAF, inhibiting its activity [103]. At this time, it is not known if any of these mitotic effects are manifested in prostate cancer.

Many of the described actions of AMPK are cytoplasmic. However, it is becoming increasingly clear that AMPK has significant functions in the nucleus, some of which may not be linked to metabolism (Figure 1). As mentioned above, AMPK can alter metabolism by directly phosphorylating and regulating histone H2B, HNF-4α and PGC-1α [39,69,75,78]. Additionally, AMPK has been demonstrated to phosphorylate and inhibit the association of the histone acetyltransferase p300 with nuclear receptors [104]. This may partially explain the reported AMPK-mediated inhibition of AR activity [105]. However, more detailed molecular and genetic studies need to be done to confirm the contexts under which this possible negative feedback occurs. This is because these findings seem to be in direct contrast to the report by Karacosta et al. that CaMKK2 potentiates AR activity to form a positive feedback loop [46]. In our hands, we have been unable to detect either agonistic or antagonistic effects of CaMKK2 and/or AMPK on AR activity (unpublished data). However, we have only examined a limited gene set. CaMKK2 and AMPK could each be regulating a subset of AR target genes which may explain the different conclusions between groups. AMPK also directly phosphorylates and stimulates the transcription factor FOXO3 [106]. AMPK-phosphorylated FOXO3 transcribes a subset of genes involved in growth arrest, autophagy and stress resistance (Figure 2). In LNCaP cells, FOXO3a contributed to apoptosis and hence, may function as a tumor suppressor in the prostate [107]. The transcription factor CREB and one of its coactivators, CRTC2, are also direct targets of AMPK [108,109]. Interestingly, AMPK appears to have opposing effects on these two proteins as AMPK-mediated phosphorylation increases CREB-dependent transcription but inhibits CRTC2. Given the complexities of the regulation of this transcriptional complex and the diverse processes CREB regulates, it is difficult to speculate what phenotypic effects this would have in prostate cancer assuming it is regulated at all in the disease. Similarly, it is difficult to predict if the reported AMPK targeting of the class IIA family of histone deacetylases will occur in prostate cancer and if so, what net effect it would have on the disease [24].

4. Existing pharmacological strategies to control AMPK signaling

As outlined in the previous sections, depending on the context and specific downstream signals activated by AMPK, it may act as a pro- or anti-cancer factor. In agreement with this, the activation of AMPK has been found to encompass anti-proliferative effects in various malignancies including breast, lung, skin and hematological cancers [110]. Whereas in prostate cancer, there is increasing evidence that AMPK signaling, and the activation of its upstream regulator, CaMKK2, are tumorigenic and stimulate glycolysis, oxidative phosphorylation, fatty acid oxidation and mitochondrial biogenesis,
providing energy and building blocks for proliferation [39,45,46]. On the contrary, it was also demonstrated that activators of AMPK, such as AICAR and the antidiabetic drug rosiglitazone, are able to diminish androgen-sensitive and CRPC cell proliferation with a consistent decrease in de novo fatty acid synthesis [111]. In contrast, the use of AICAR was able to rescue the growth inhibition initiated by the siRNA targeted downregulation or chemical inhibition of CaMKK2 [45]. These inconsistent reports might be derived from the additional non-AMPK specific impact of AICAR. AICAR is converted intracellularly into an AMP mimic [112] that, apart from stimulating AMPK, possesses inhibitory effects on adenylyl cyclase and fructose-1,6-bisphosphatase, thereby potentially contributing to the antiproliferative activity seen in prostate cancer [113,114].

A recent article comparing the effects of six AMPK agonists (metformin, phenformin, AICAR, salicylate, 2DG and A-769662) in wild-type and AMPKα1/α2 knockout HEK293 cells, reported that only A-769662 exerted anti-proliferative effects exclusively via the activation of AMPK, whereas no agonists possessed AMPK-dependent effects on viability, anchorage-independent growth and glycolysis [115]. Intriguingly, cell death and caspase-3 activation initiated by these ‘agonists’ was augmented in cells lacking functional AMPK [115]. These agents have long been used to elucidate the role of AMPK in various tumors including prostate cancer, however, this study questions the validity of such experiments.

Most recently, a molecular screening identified a new compound, MT 63-78, as a specific allosteric activator for AMPK. MT 63-78 greatly reduced the proliferation of various cancer cells in vitro as well as the growth of androgen-sensitive tumors in vivo [116]. It is therefore feasible that a substantial increase in the activation of AMPK confers anti-proliferative effects. Although, it is not fully established how this compound would affect the cellular metabolism of non-cancerous cells. As described previously, continuous moderate activation of the AR-CaMKK2-AMPK pathway promotes malignant transformation of the prostate. Therefore, agonistic manipulation of AMPK should be carefully reconsidered.

One of the most controversial drugs in regard to specificity on AMPK activity is the commonly used anti-diabetic agent metformin. Metformin has been extensively studied for its potential use in the treatment of various malignancies [117-120]. It has subsequently been revealed that the action of metformin on hepatic gluconeogenesis is independent of LKB1-AMPK signaling [121]. Additionally, metformin’s antitumor actions in prostate cancer appear to involve various molecular events that are not related to AMPK signaling [122-124]. Profiling of AICAR- and metformin-induced changes in the transcriptome of LNCaP prostate cancer cells revealed only ~8% of common genes that were up- or down-regulated by both drugs, further indicating distinct mechanisms of action of these compounds [105]. This is likely derived from metformin’s indirect regulation of AMPK; by inhibition of the mitochondrial respiratory-chain complex 1, metformin lowers cellular energy, consequently elevating the level of AMP, leading to the activation of AMPK [125]. In a study by Sahra et al., metformin inhibited the proliferation and clonogenicity of LNCaP and PC3 cells in vitro, and reduced the tumor growth of LNCaP xenografts by 55%. They also identified a major difference in the antiproliferative effects of AICAR and metformin; whereas AICAR induced apoptosis, metformin triggered a cell cycle G0/G1 arrest and decreased expression of the cell cycle regulators cyclin D1 and E2F1 and suppressed the phosphorylation of pRb all mainly through an AMPK-independent pathway [123]. A subsequent study further demonstrated metformin’s anti-proliferative effects were mediated in an AMPK-independent manner by the activation of REDD1, a negative regulator of the mTOR complex [124].

Observational studies investigating the incidence of prostate cancer and related mortality in diabetic men receiving metformin have provided conflicting results. Several population-based studies reported significantly improved survival rates with the use of metformin [126,127]. Most intriguingly, Margel et al. presented a 24% decrease in prostate cancer-specific mortality for every 6 months of metformin treatment [127]. However, multiple reports have subsequently warned about numerous methodological issues that may amplify the advantage of metformin in this study [128,129]. In addition, other studies did not find a correlation between metformin and the incidence of prostate cancer [130-132] or importantly, in some cases they presented a significantly increased risk of mortality with the use of metformin [129,133,134]. Collectively, these retrospective studies do not fully support the implementation of metformin in the treatment of prostate cancer. Nonetheless, various controlled clinical trials are in progress to test metformin alone or in combination with castration, simvastatin, docetaxel or anti-androgen therapy that may provide definitive answers regarding the possible use of metformin in prostate cancer [135]. So while the anti-tumor effects of metformin may not be related to AMPK activation in prostate cancer, patients may still benefit from its use. The possible efficacy of metformin in various malignancies is expected to be deciphered in the next few years.

The antitumor effects of various natural compounds has been linked to the activation of the AMPK pathway along with various other intracellular effects. The hydrolysis product of a glucosinolate found in cruciferous vegetables, B-DIM, effectively stimulates the phosphorylation of AMPK and its downstream targets raptor and ACC, but inhibits the phosphorylation of mTOR in C4-2B and LNCaP cells in a concentration-dependent manner [136]. However its antiproliferative effects have been linked to diverse actions including a p38 MAPK-dependent G1 cell cycle arrest and apoptosis [137,138]. Salicylates that are known to possess anti-inflammatory properties through the inhibition of cyclooxygenase-2 also activate AMPK by direct binding to the β1 subunit [139]. Continuous administration of low dose aspirin has been associated with a decreased risk of prostate cancer [140] although other
studies have failed to demonstrate this correlation [141,142].
Another highly promising natural compound found in red
wine, resveratrol, was shown to trigger AMPK activation
indirectly through the SIRT1-LKB1 pathway [143]. However,
its applicability in prostate cancer treatment is questionable since
preclinical testing found no major inhibition on the growth of
tumor xenografts and further was correlated with increased
angiogenesis and decreased survival [144,145]. Several other com-
ounds, such as quercetin, berberine and epigallocatechin 3-gal-
late have been claimed to act via AMPK-activation, but later were
all shown to have pleiotropic cellular effects [146].

An increasing body of evidence suggests that pharmacolog-
ical inhibition, rather than stimulation of AMPK signaling
might represent a valuable strategy for the treatment of pro-
cate cancer. Compound C, which is widely used in experi-
mental settings for the selective inhibition of AMPK activity,
greatly reduces the proliferation of prostate cancer cells [40]. However, like many other ‘AMPK modulators’,
compound C has been recently shown to target multiple path-
ways independent of AMPK [147]. Unfortunately, the number of drugs available for the specific inhibition of AMPK is very
limited but the discovery of new compounds with this quality is anticipated in the next few years. Alternatively,
phar-maceu-
tical manipulation of CaMKK2 activity may also provide an
effective strategy to block AMPK signaling. As highlighted
above, CaMKK2 is up-regulated in prostate cancer and its
expression is triggered by AR signaling [29,45]. A specific,
cell-permeable inhibitor of CAMKK, STO-609, has been
available since 2002 [148]. Correspondingly, inhibition of
CaMKK2 activity by STO-609 reduced cell proliferation and growth of androgen-sensitive and castration-resistant
tumors [45] and significantly inhibited the androgen-induced
migration of LNCaP cells [29]. Moreover, STO-609 signifi-
cantly attenuated glucose uptake and lactate secretion [45].
STO-609 has a low clearance, shows no accumulation with
repeated dosing and is effectively taken up by the tumors,
whereas it has no detectable effects on normal prostate [45].
Therefore, STO-609, or a derivative of STO-609, may be a
good candidate to evaluate if the pharmacological suppression
of the CaMKK2-AMPK pathway provides clinically-relevant
benefits to patients with prostate cancer. Although, it is cur-
rently unknown if these trials are being scheduled.

5. Conclusion

In summary, the AMPK pathway possesses an oncogenic role
in prostate cancer by regulating metabolic adaptation as well
as migration, autophagy and the cell cycle. Many aspects of
oncogenic AMPK signaling described in this review have
only been established in healthy cells, even though they are
likely to occur in prostate cancer and facilitate malignancy.
Further investigation of these molecular processes in prostate
cancer should be exploited. We hope to encourage such stud-
ies by providing the present mechanistic review.

6. Expert opinion

Ultimately, AMPK’s role in prostate cancer will largely be
governed by three interconnected aspects. First, the type of
AMPK signaling will be dictated by the stimulus. In this
regard, general stress signals like low ATP levels or pharmaco-
logical drugs that possess widespread activities will, in addi-
tion to activating numerous other stress signaling cascades,
activate the global cellular AMPK pool leading to a diverse,
often counterproductive chain of events. This would be in
contrast to the CaMKK2-mediated activation of AMPK. In
this scenario, only a subpopulation of AMPK that makes
direct interactions with the upstream kinase would be acti-
vated, likely leading to a more controlled response.

Second, the AMPK trimer composition matters. For example, it has been demonstrated that the α1 and
α2 catalytic subunits have distinct subcellular locations [149].
While the α2 subunit is mostly restricted to the nucleus, the
α1 subunit is more cytoplasmic. As such, α1 would be
the more likely target for cytoplasmic upstream kinases like
CaMKK2. Further, α1 is the predominant catalytic AMPK
subunit found in the prostate [150] and in prostate cancer
cells [29]. This is important to consider given the two different
subunits may dictate pro-tumor versus anti-tumor phenotypes.
Correspondingly, AMPK’s reported effects in the
nucleus are often associated with tumor suppressive functions
(e.g., p300 inhibition, p53, p21 and p27 induction, etc.).
Hence, AMPK α1 may have a more oncogenic role while
AMPK α2 more closely resembles a tumor suppressor. These
apparent differences may help explain why some groups that
have genetically-deleted the α2 subunit observe increased
transformation and tumor growth under certain contexts
while targeting the α1 subunit alone or jointly with
α2 inhibits transformation, prostate cancer cell proliferation,
migration and survival [29,39,40,86,87,116,151-154].

Last, the type of AMPK complex that is activated will influence
which downstream targets are modified. It is unlikely
that the same sets of downstream targets will be activated/
inhibited by different AMPK stimuli and trimer complexes.
This is of further importance because the identification of
the downstream drivers may also yield better therapeutic tar-
gets. Therefore, defining the specific processes that are tar-
geted by AMPK under different conditions will be critical to
understanding if, how and when to target AMPK for the
treatment of prostate cancer.

Accumulating evidence suggests that AMPK may be a key
survival factor for tumor cells, facilitating adaptation during
starvation and stress. Tumor cells may increase their resistance
to stress by up-regulating AMPK activity. Selection for this
acquired adaptability could contribute to the development of
castration-resistance during androgen-ablation therapy.
This idea is supported by the increased activation of the
CaMKK2-AMPK pathway seen in CRPC [39,45,48]. Development
of the castration-resistant disease is linked to several
mechanisms including the increased production of intraprostatic androgens or mutations generated in the AR gene resulting in constitutive ligand-independent activity [155]. It is our opinion that the CaMKK2-AMPK pathway, as a downstream messenger of AR activation, is a valuable target for the inhibition of AR-mediated metabolic adaptation in both androgen-sensitive and CRPC.

In addition to the various unidentified aspects of AMPK signaling in prostate cancer, another factor that complicates the development of a targeted therapy is the lack of a safe and effective specific AMPK inhibitor. Since CaMKK2 appears to be the predominant AMPK-activating kinase in prostate cancer, and its inhibition successfully suppresses the growth of tumors in preclinical models of prostate cancer [29,45], CaMKK2 inhibitors may have utility in the treatment of prostate malignancies. Although, it should be noted that CaMKK2 plays an important neuroprotective role in the brain [156]. Therefore, CaMKK2 inhibitors should not be able to pass the blood-brain barrier. However, advances in medicinal chemistry will likely be able to address this common drug development problem prior to any human trials.

The antitumor effects of AMPK activators in preclinical tests are thought to be caused, at least in part, by an inhibitory action on the mTORC1 complex, thereby promoting autophagy and apoptosis [90,116]. Considering the potential risk of stimulating diverse protumor processes in parallel with the antitumor effects, we suggest the use of mTOR-specific inhibitors, such as the rapamycin analogs, could be combined with blockade of the CaMKK2-AMPK pathway. This may be especially relevant in prostate cancers, which have recently been demonstrated to exhibit increased levels of a TSC2 splice variant that lacks the inhibitory action on mTOR, along with a concomitant decline in levels of the full-length mTOR inhibitor protein [96].

In summary, we propose that inhibitors of the CaMKK2-AMPK pathway, alone or in combination with androgen-ablation therapy or chemotherapy, could represent a future strategy in the treatment of prostate cancer. Alternatively, elucidation of the relevant processes downstream of AMPK that are driving cancer progression may yield a number of new therapeutic targets. Collectively, these approaches would limit metabolic adaptation, the occurrence of castration resistance and the metastatic potential of prostate cancer cells.

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Declaration of interest

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Affiliation
P. Popovics1,2,3
D. Daniel E Frigo4,5
Andrew V Schally1,6,7 & Ferenc G Rick1,8 MD PhD
1,7Authors for correspondence
1Veterans Affairs Medical Center and South Florida Veterans Affairs Foundation for Research and Education, Research (151) 2A127, 2A127, 1201 NW 16th St, Miami, FL 33125, USA
Tel: <1 305 5753477;
Fax: <1 305 5753126;
E-mail: ferencrick@gmail.com
2University of Miami, Miller School of Medicine, Division of Cardiovascular Diseases, Department of Medicine, Miami, FL 33136, USA
3Department of Medicine III, Medical Faculty Carl Gustav Carus, D-01307 TU Dresden, Germany
4University of Houston, Center for Nuclear Receptors and Cell Signaling, Department of Biology and Biochemistry, Houston, TX 77204, USA
5University of Houston, Miller School of Medicine, Division of Hematology/Oncology, Department of Medicine, Miami, FL 33136, USA
6University of Miami, Miller School of Medicine, Division of Endocrinology, Department of Medicine, Miami, FL 33136, USA
7Florida International University, Herbert Wertheim College of Medicine, Department of Urology, Miami, FL 33199, USA