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New strategies in Prostate Cancer: targeting lipogenic pathways and the energy sensor AMPK

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Abstract

Whereas the role of Metabolic Syndrome (MS), and a high fat diet in prostate cancer (PCa) risk is still a matter of intense debate, it is becoming increasingly clear that obesity can cause perturbations in metabolic pathways that contribute to the pathogenesis and progression of PCa. Moreover, prostate epithelial cells *per se* undergo a series of metabolic changes, including an increase in *de-novo* lipogenesis, during the process of tumor formation. These metabolic alterations, at both the cellular and organismal levels, are intertwined with genetic aberrations necessary for neoplastic tranformation. Thus, altered metabolism is currently subject to intense research efforts and might provide preventative and therapeutic opportunities, as well as a platform for biomarker development. In this article, we review evidence that the metabolic sensor 5'-AMP-activated protein kinase (AMPK), which physiologically integrates nutritional and hormonal signals and regulates cell survival and growth-related metabolic pathways to preserve intracellular ATP levels, represents a link between energy homeostasis and cancer. Thus, when AMPK is not activated, as in the setting of MS and obesity, systemic metabolic alterations permissive to the development of PCa are allowed to proceed unchecked. Hence, the use of AMPK activators and inhibitors of key lipogenic enzymes may represent a promising therapeutic strategy for PCa.

BACKGROUND

Prostate Cancer (PCa) is the most commonly diagnosed malignancy in men and the second leading cause of cancer-related death in industrialized countries. The main risk factors for this disease are age, black race, family history. Patients with metastatic PCa initially respond to androgen deprivation (AD) therapy for a median time of 12–18 months (1), following which the majority of patients relapse with castrate-resistant disease, which is associated with high morbidity and mortality. Chemotherapeutic treatment options for castrate-resistant PCa have a very modest palliative and survival benefit, so there is clearly an urgent need for additional therapies.

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In the era of targeted therapies, many clinical trials have been conducted to test targeted drugs in PCa with the objective of studying their effects either on advanced metastatic disease or on primary tumor (neoadjuvant and surveillance trials). There is now growing interest in targeting metabolic pathways that may be altered during prostate tumorigenesis and PCa progression.

This review briefly discusses the impact of high-fat diet and the Metabolic Syndrome (MS) as well as obesity on PCa risk. In addition, some potential mechanistic aspects and intracellular metabolic consequences that might contribute to prostatic carcinogenesis will be discussed. In particular, activation of lipid metabolism has been described in most localized and metastatic prostate tumors, underscoring its potential role in tumorigenesis and tumor progression. Here, we describe the crucial role of AMPK as master regulator of lipogenic pathways as well as of intracellular oncogenic signaling [i.e. mammalian target of rapamycin (mTOR) pathway]. We therefore propose the activation of AMPK as a potential therapeutic strategy in PCa.

ON THE HORIZON

Dietary intervention

The incidence and disease-specific mortality of PCa show marked geographic variation, being greatest in North America and Western Europe, and lowest in Asia (2). These differences undoubtedly have a genetic component, but the relative contribution of diet and the “Western lifestyle” to PCa development has not been elucidated (3). Numerous epidemiological studies support an association between dietary fat intake (particularly saturated fats) and PCa risk (4, 5), unfavorable prognosis, and relapse after treatment for localized PCa (6). In addition, differential gene expression of human prostate xenografts from mice under high-fat diet, showed significant upregulation of insulin-like growth factor 1 receptor (IGF-1R), a known driver of prostatic carcinogenesis, compared to mice under low-fat diet (7). Importantly, however, activating mutations in the IGF-1/phosphoinositol-3-kinase (PI3K) pathway may influence the response of cancers to dietary restriction-mimetic therapies (8). Nevertheless, more recent studies seem to refute these previous observations (9, 10). Thus, the existence of a relationship between fat intake and PCa risk still remains an intriguing open question.

The influence of dietary fat on PCa has been linked to specific fatty acids (FA): several *in-vivo* studies have indicated that low-fat diets high in omega-3 (n-3) polyunsaturated FA (PUFAs) reduce the development and progression of PCa, whereas high-fat diets rich in omega-6 (n-6) promote the growth and proliferation of PCa cells (11). Since the “Western diet” contains a disproportionally high n-6/n-3 ratio, n-6 PUFAs are likely to be critical modulators of human prostate carcinogenesis. The tantalizing epidemiological data, combined with the positive effects of n-3 PUFAs in cell culture and animal models, prompted the development of clinical trials using n-3 PUFAs in the prevention and treatment of PCa (http://clinicaltrials.gov/). To date, five clinical trials (NCT0099674, NCT00253643, NCT00458549, NCT00433797, and NCT00402285) are ongoing, and one (NCT00049309) has been successfully completed showing that flaxseed supplementation reduces PCa proliferation rates in men presurgery (12).

Obesity, Metabolic syndrome and PCa

Epidemiological studies—In spite of the controversial association between high-fat diet and PCa risk, there is mounting epidemiologic evidence for a relationship between obesity and PCa progression. Obesity has been identified as an important adverse prognostic factor for PCa (13). Moreover, population studies have revealed that PCa patients with higher

serum levels of insulin or c-peptide are at increased risk of adverse outcome (14). The mechanism that underlies the association between obesity and PCa is not clear, but insulin-mediated increase of IGF-1 and the subsequent activation of PI3K/mTOR pathway have been suggested (15). Obesity has also been associated with decreased serum levels of the adipocytes-secreted cytokine adiponectin. Recent epidemiological studies showed an inverse correlation between adiponectin levels and the risk of PCa (16, 17) and *in vitro* studies confirmed adiponectin's inhibitory effect on PCa cell growth through activation of AMPK (see below) (18). Moreover, abdominal obesity is frequently associated with MS, a state of metabolic dysregulation characterized mainly by insulin resistance, hyperglycemia, dyslipidemia, hypertension, and predisposition to type II diabetes (19). Even if some studies have shown its association with a higher risk of PCa (20–22), the results are still inconclusive (23, 24). This may be due to a lack of unambiguous definition of MS, differences in age at baseline measurement and length of follow up. In fact, a recent study of ours has shown that MS as defined by strict accepted international definitions, is significantly associated with prostate cancer mortality when the competing risk of early death from other causes, is taken into account (25).

5'-AMP-activated protein kinase (AMPK)—AMPK is a highly conserved energy-sensing serine/threonine kinase, consisting of a α catalytic subunit and regulatory β and γ subunits. At the cellular level, AMPK is activated by metabolic stressors that deplete ATP and increase AMP (e.g. exercise, hypoxia, glucose deprivation). At the level of the organism, enzyme activity is also under the control of hormones and cytokines, such as adiponectin and leptin (26). Activation of AMPK reduces plasma insulin levels, suppresses ATP-consuming metabolic functions (such as synthesis of FAs, sterols, glycogen, and proteins), and increases ATP-producing activities (glucose uptake, FA oxidation, and mitochondrial biogenesis) to restore energy homeostasis. Thus, AMPK functions as a central metabolic switch that governs glucose and lipid metabolism.

Decreased AMPK activity has been found to contribute to the metabolic abnormalities involved in MS (15, 27). Moreover, a recent study revealed an association between polymorphisms in the PRKAA2 gene (encoding the α2 subunit of AMPK, which is responsible for the MS phenotype) (28) and susceptibility to insulin resistance and diabetes in the Japanese population (29). Interestingly, the same locus correlates with PCa risk (30), suggesting that AMPK dysregulation may provide a mechanistic link between MS and PCa. Consequently, drugs that ameliorate MS conditions through AMPK activation (Table 1) may be beneficial for PCa prevention and treatment.

Metformin: current and new prospectives—Metformin is a biguanide used as mainstream therapy for type II diabetes for its insulin-sensitizing effects. It has been shown to prevent or delay the onset of MS (31). Recent evidence indicates that: a) diabetics under treatment with metformin show a reduced cancer incidence (32) and cancer-related mortality compared to patients exposed to sulfonylureas or insulin (33); b) metformin use is associated with a 44% risk reduction in PCa cases compared to controls in Caucasian men (34); c) breast cancer patients treated with neoadjuvant chemotherapy and metformin have significantly higher pathologic complete responses than patients not taking metformin (retrospective study) (35). Thus, its potential antineoplastic activity has been proposed and it is currently under investigation. These human studies are further supported by studies *in vitro* and in xenograft models, showing its antitumor activity on PCa cells (18, 36) and by the exciting discovery that metformin is able to selectively kill cancer stem cells from 4 genetically distinct breast cancer lines (37). The mechanism of action for metformin's anti-tumor effect is not completely understood and has been ascribed to both direct and indirect effect. Metformin's *direct* effects on tumor have been partly attributed to AMPK activation (38). At millimolar concentrations, metformin inhibits complex I of the respiratory chain

resulting in increased AMP/ATP ratio and secondary activation of the AMPK pathway (39). This results in inhibition of mTOR and p70S6kinase 1 (S6K1) activity and decreased translational efficiency in PCa cell lines (36). However, inhibition of AMPK using siRNA did not prevent the antiproliferative effect of metformin in PCa cell lines, suggesting that its effects can be independent of AMPK. This could be partly explained by induction of G0/G1 cell cycle arrest, which was accompanied by a strong decrease in cyclin D1 protein level, pRb phosphorylation and an increase in $p27^{kip}$ protein expression (36). *In vitro* studies have also shown that metformin may inhibit tumor growth by preventing p53-induced autophagy (40) and its treatment has an inhibitory effect on nuclear factor-kappa B (NF-κB) and extracellular regulated-signal kinase (Erk) 1/2 activation by an AMPK-independent mechanism (41). Metformin's *indirect* effect on tumor proliferation can be explained via inhibition of hepatic gluconeogenesis and increased glucose uptake in skeletal muscle, thereby decreasing circulating glucose, insulin and IGF-1 levels, and resultant signaling flux through the insulin/IGF-1 pathway (42).

Understanding how biguanides mediate their anti-cancer effect is critical before launching clinical trials for advanced disease. If anti-tumor effects are mediated by AMPK pathway, a specific group of PCa patients with low AMPK activation might be targeted in clinical trials with biguanides. Alternatively, if the anti-tumor effects of biguanides are predominantly by an indirect mechanism, then PCa patients most likely to benefit might be those with concomitant insulin resistance. Therefore, although metformin is very safe and remarkably inexpensive, it is critical to understand its mechanism of action in PCa before embarking on trials in metastatic disease.

A phase II clinical trial is currently ongoing to study the effect of neoadjuvant metformin therapy in PCa patients prior to radical prostatectomy (NCT00881725). In addition, a randomized phase II surveillance trial to test the combinatorial effect of the 5-alpha-reductase inhibitor dutasteride and metformin in low risk PCa patients, not previously treated, has also been planned at Dana Farber Cancer Institute, Boston.

Anti-metabolic approaches to target PCa cells

Prostate cancer cell likely require specific metabolic alterations that cooperate with "driver" genetic events to effect neoplastic transformation and tumor progression. Increased aerobic glycolysis has been found only in advanced disease whereas exacerbation of *de-novo* FA and sterol synthesis due to overexpression of key enzymes [ATP citrate lyase (ACLY), Acetyl-CoA carboxylase (ACC), fatty acid synthase (FASN), 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA reductase)] and increased protein synthesis due to hyperactivation of mTOR are common features of both primary and advanced PCa (43–46). These alterations are induced both by androgens and by the activated PTEN/PI3K/Akt/mTOR pathway, deregulated in a significant number of PCa. Indeed, deletions/mutations in the tumor suppressor phosphatase and tensin homologue (PTEN) are found in 30% of primary PCa and in over 60% of metastatic PCa (47). Hence, inhibitors of mTOR and PI3K, alone or in combination with chemotherapeutic agents, are being tested in hormone-refractory PCa (48). At the same time, the observation of increased *de-novo* FA and sterol synthesis has led to increasing efforts to develop inhibitors of these metabolic pathways.

Inhibitors of lipogenesis—ACC, FASN and HMG-CoA reductase are responsible for the synthesis of malonyl-CoA, the saturated FA palmitate, and mevalonate (the precursor of cholesterol), respectively and their role in the pathogenesis and progression of PCa is well established (49, 50). Small molecule FASN inhibitors (cerulein, C75, C93, Orlistat), HMG-CoA reductase inhibitors (statins), and ACC inhibitors (such as soraphen A) have shown promising preclinical results both *in vitro* and *in vivo* (51–53). So far, the use of FASN

inhibitors as systemic drugs has been hampered by pharmacologic limitations and side effects (weight loss) (51). However, recent reports have described new potent FASN inhibitors identified through high-throughput screening as a testimony of the continuous interest for FASN as a therapeutic target (51). Moreover, recent data showed a reduced incidence of PCa among statin users in the Finnish Prostate Cancer Screening Trial, associated with lower PSA levels (54). This evidence suggests that interfering with lipid metabolism represents an important direction to pursue. At present, two clinical trials are ongoing to investigate the effect of statin therapy prior prostatectomy (NCT00572468) or during external beam radiation therapy (NCT00580970). A more accurate stratification of patients eligible for lipogenic pathways-inhibiting therapies could be achieved thanks to the increasing development of new positron emission tomography (PET)-based metabolic imaging techniques. In fact, lipid metabolism is being investigated by ^{11}[C]- and ^{18}[F]-labeled acetate or choline. Both these tracers have shown increased sensitivity in the detection of both primary, recurrent and metastasic PCa (55).

Direct AMPK activators—One of the major impediments in the development of targeted therapies is the crosstalk between multiple signaling and metabolic pathways that can result in functional redundancy to maintain cell growth and survival circuits. One strategy to overcome this obstacle is represented by the combinatorial approach to targeted therapies. Another approach may be to target a master regulatory switch of major oncogenic signaling and metabolic pathways, such as AMPK.

The major kinase involved in AMPK activation is the well-known tumor suppressor LKB1 (56). LKB1 germ-line mutations are responsible for Peutz-Jegher syndrome, predisposing carriers to hamartomas and a variety of malignant epithelial tumors (57). Interestingly, over 80% of LKB-1 knock out mice appear to develop prostate intraepithelial neoplasia (PIN) (58). This suggests that the LKB1-AMPK pathway may act as the link between cancer and energy homeostasis. Indeed, when physiologically or pharmacologically activated, AMPK acts in a tumor suppressor-like fashion. It inhibits key lipogenic enzymes by direct phosphorylation (ACC, HMG-CoA reductase) or by transcriptional regulation (ACLY, FASN) through the suppression of the transcriptional factor Sterol Regulator Element Binding Protein 1 (SREBP-1). In addition, AMPK inhibits the mTOR pathway through direct phosphorylation of Tuberous sclerosis complex 2 protein and the mTOR-associated factor Raptor (Figure 1). Finally, it induces cell cycle arrest or apoptosis through phosphorylation of p53 and FOXO3a (59). Thus, activated AMPK can switch off multiple oncogenic pathways at once. In particular, it may simultaneously inhibit the two major pathways (lipogenic and PI3K/mTOR pathways) that drive PCa carcinogenesis antagonizing the activity of Akt at multiple levels (SREBP-1, TSC-2, and mTOR complex 1 level). Consequently, AMPK activators, overcoming the feedback activation loop of Akt following long-term mTORC1 inhibition (likely responsible for the clinical failure of mTORC1 inhibitor Rapamycin) (60), may be effective in metastatic PCa harboring PTEN deletions. Hence, intense efforts are being made to directly activate AMPK. The direct AMPK activator Aminoimidazole-4-carboxamide-1-β-D-ribofuranoside (AICAR), an AMP mimetic, has been shown to inhibit PCa cells proliferation (61) and tumor growth in PCa xenograft models (36). However, AICAR is not entirely specific for AMPK, it has limited oral bioavailability and frequently induces an increase in blood levels of lactic acid and uric acid. The possibility of novel small molecules able to allosterically activate AMPK has been greatly fostered by the recent publication of the crystal structure of AMPK's subunits (62). Abbott laboratories has pioneered this area and identified A-769662, a thinopyridone AMPK activator that activates the enzyme by binding the β1 subunit (63). A-769662 has been shown to delay tumor development and decrease tumor incidence in PTEN+/− mice with a hypomorphic LKB1 allele (64). A second small molecule activator (PT1), not yet well characterized, has also been recently reported (65).

CONCLUSION

The current paradigm in personalized cancer therapeutics is to target oncogene-addicted pathways in individual tumors. As highlighted in this review, the cellular and whole-organism metabolic *milieu* can be exploited to interfere with PCa cells using a "synthetic lethal" strategy by combining inhibitors of metabolic enzymes with targeted inhibitors of mutated oncogenes. Furthermore, obtaining broad-based metabolite profiling of prostate tumors by mass spectrometry and/or nuclear magnetic resonance technologies will help develop novel functional PCa classifications based on deregulated metabolic pathways. This, in combination with genetic and proteomic mapping, could be exploited to achieve more accurate subclassification of PCa, new metabolism-based functional imaging techniques, as well as more effective therapies based on targeting metabolic enzymes.

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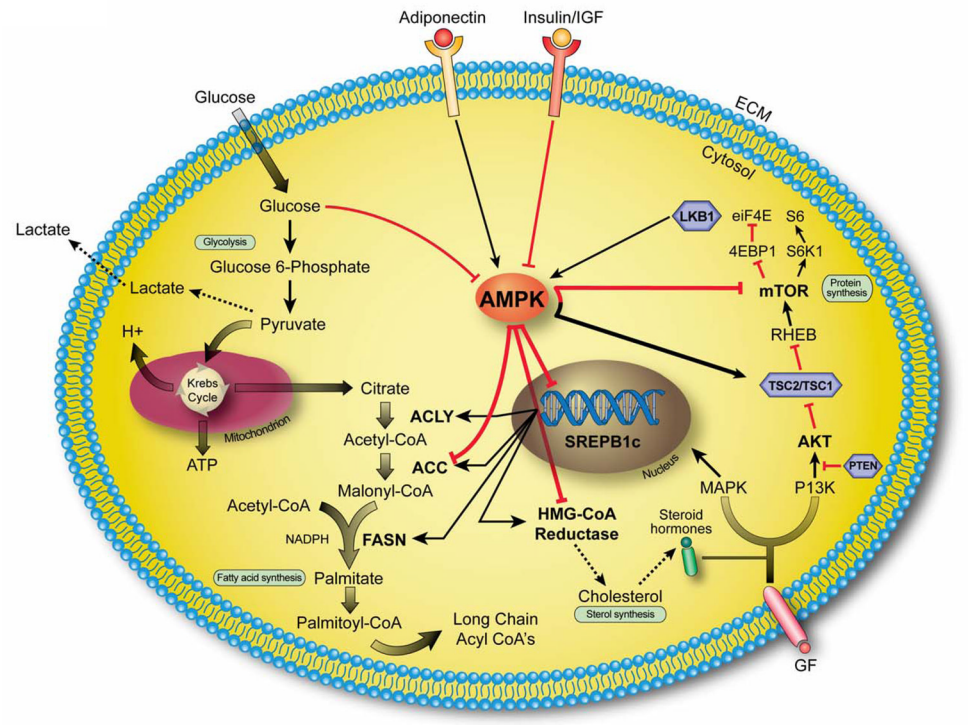

Figure 1. AMPK controls main metabolic pathways in PCa cells

PCa cells are characterized by exacerbation of lipogenesis associated with hyperactivation of mTOR pathway. Activation of AMPK can inhibit these pathways by direct phosphorylation of key lipogenic enzymes [ACC, in particular isoform 1, HMG-CoA reductase} and key kinases (the complex TSC1/TSC2 and the mTOR-associated factor Raptor) or by regulating transcription through SREBP1c. Red and black arrows indicate activation and inhibition, respectively. Tumor suppressor genes are represented in violet hexagonal boxes. AMPK= AMP-activated protein kinase, SREBP1c= Sterol regulatory element binding protein-1c, ACLY=ATP citrate lyase, ACC= Acetyl-CoA carboxylase, FASN= Fatty acid synthase, HMG-CoA reductase=3-Hydroxy-3-methyl-glutaryl-CoA reductase, MAPK= mitogen-activated protein kinase, PI3K= phosphatidylinositol-3-kinase, PTEN= phosphatase and tensin homolog, TSC2/TSC1= tuberous sclerosis complex 1/2, RHEB= Ras homolog enriched in brain, mTOR= mammalian target of rapamycin, 4EBP1= 4E-binding protein 1, S6K1= S6 kinase 1, eiF4E= Eukaryotic translation initiation factor 4, GF=growth factors.

Table 1

Current direct and indirect AMPK activators

Activator	Effect on AMPK	Mechanism
Metformin	indirect	Increase AMP/ATP by inhibition of complex 1 of mitochondrial respiratory chain
TZDs*	indirect	Increase PPARγ-mediated release of adiponectin, which consequently activates AMPK
Deguelin	indirect	Not fully clarified. Decrease of ATP
Epigallocatechin-3-gallate	indirect	Activation of the AMPK activator CaMKK**
Barberin	indirect	Increase AMP/ATP by inhibition of mitochondrial function
α-Lipoic acid	indirect	n.d.
Resveratrol	indirect	Not fully clarified. Possible activation of SIRT1*** and consequent deacetylation of the AMPK activator LKB1
AICAR ****	direct	AMP mimetic
A-769662	direct	Allosteric binding of β1 AMPK subunit
PT1	direct	Allosteric binding of α1 AMPK subunit

n.d.= not determined yet,

* TZDs= thazolidinediones,

** CAMKK= Calmodulin-dependent protein kinase kinase,

*** SIRT1= sirtuin 1,

**** AICAR= 5-Aminoimidazole-4-carboxamide-1-b-riboside.