Review Article

Linking cellular metabolism and metabolomics to risk-stratification of prostate cancer clinical aggressiveness and potential therapeutic pathways

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Abstract: Prostate cancer treatment is based on the stratification of disease as low-, intermediate- or high-risk. This stratification has been largely based on anatomic pathology of the disease, as well as through the use of prostate specific antigen (PSA). However, despite this stratification, there remains heterogeneity within the current classification schema. Utilizing a metabolic approach may help to further establish novel biomolecular markers of disease aggressiveness. These markers may eventually be useful in not only the diagnosis of disease but in creating tumor specific targeted therapy for improved clinical outcomes.

Keywords: Prostatic neoplasms; metabolomics; metabolism; therapies, investigational; metabolic networks and pathways; precision medicine

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Introduction

A long-observed phenomenon among prostate cancers is the heterogeneity in severity and prognosis. Prostatic adenocarcinoma is the most commonly diagnosed non-cutaneous cancer in American men. In 2014, 172,258 men in the United States were diagnosed with prostate cancer, attributing to 28,343 deaths (1). This discrepancy in prevalence versus mortality exemplifies the heterogeneity of tumor aggressiveness and responses to treatment modalities seen in prostate cancer. The difference in incidence versus mortality has recently led to a debate about the presumptive overtreatment of low-risk disease. Surrounding the debate has been the use of prostate specific antigen (PSA) as a cancer marker (2). It has been asserted that utilizing PSA may have led to over-diagnoses and treatment of indolent cancers. Overtreatment of low-risk disease greatly increases treatment-related morbidity in a population that may be adequately managed with active surveillance. Interestingly, there is now also a concern that this push away from overtreatment might also sway the field towards under-treatment of patients with aggressive disease (3).

A reliable and accurate method to stratify the risk of prostate cancer at the time of initial diagnoses would allow for a reduction in morbidity for those with intermediate- or low-risk disease and more aggressive treatment for patients with high-risk disease. As the majority of deaths from prostate cancer stem from those patients with the aggressive, high-risk disease, better understanding of this particular subset of tumors may have a large effect in decreasing prostate cancer mortality (4).

High risk prostate cancer

The initial step in the treatment of high-risk prostate cancer is to first define such a disease. The term high-risk prostate cancer refers to a cancer that is anticipated to recur despite optimal local therapy (5). It has been extrapolated that high-risk prostate cancer represents around 15% of all prostate

cancer diagnoses (5). However using this working definition, the cases are stratified largely after treatment failure or when diagnoses are made late in the course of disease. By better being able to designate cancer as aggressive early in the course of disease, treatment outcomes likely will improve. Certain trends have been observed regarding who is more at risk for high-risk prostate cancer, including age at diagnosis among others (5). However the use of metabolic features of disease has not yet been incorporated into standard clinical practice.

There are multiple risk-stratification schemata to characterize prostate cancer. The American Urological Association adopted a definition of high-risk prostate cancer that was proposed by D'Amico *et al.* which categorized high-risk as a pre-operative PSA >20 and/or a pre-operative Gleason score of 8–10 and/or a clinical stage ≥T2c (6). While these factors have been associated with more aggressive cancer phenotypes, there remains heterogeneity within cancers fitting this description (7). As such, to alter this stratification schema utilizing a molecular and metabolic phenotype may produce more accurate assessments at the time of initial diagnosis.

Treatment of high-risk prostate cancer

An area of active research is focused on better understanding the differing nature of indolent and aggressive disease, as the treatment varies greatly between the two. Treatment of prostate cancer usually begins with simple observation via active surveillance (8). In intermediate to higher risk disease, definitive therapy revolves around the surgical option of prostatectomy or radiation therapy (9). Confidently defined and confirmed low-risk disease may be managed adequately with active surveillance based on a variety of factors including the patient's age, PSA, grade of the cancer, and tumor volume. While definitive surgical options may put a patient's mind at ease, it has been shown to not be necessary for all patients and comes with the risk of overtreatment and unnecessary morbidity, with no survival benefit. Furthermore, in some patients, combined approaches using systemic androgen deprivation therapy, radiation, and/or surgery may be most effective. Some progress has been made on the use of molecular characterization such as using gene expression profiles to risk stratify patients likely to benefit from such multi-disciplinary approaches (10). More accurate molecular prognostic indicators, perhaps from metabolic features of the malignancy may add more data on who benefits most from surgical intervention.

Metabolomics and cancer research

An expanding field within cancer research is that of metabolomics. By better understanding how cancer cells create and consume energy, one might discover markers to diagnose disease as well as potential therapeutic targets. It has been understood for years that malignant cells change the way in which they process energy by altering their metabolic profile (11). Progress has been made in identifying these metabolic differences. However, true insight into how these alterations occur is limited. An active area of research is focused on better understanding these processes and clinically applying the new information. This paper describes the current understanding of prostate cancer metabolism and how it relates to high-risk disease (12).

Methods

A review was conducted of peer-reviewed publications and verified epidemiologic data. Web searches were performed on PubMed using the keywords "prostate metabolism", "prostate metabolomics", "prostate cancer risk stratification" and "prostate cancer aggressiveness". Reference lists of selected articles were also reviewed to identify pertinent studies and book chapters. The search was limited to papers published after December 31, 2002. The website of the Center for Disease Control was used to provide prostate cancer statistical data.

Hallmark metabolic changes in prostate cancer

Citrate/zinc

Perhaps the most well understood metabolic phenotype of prostatic cells is related to zinc and citrate. Healthy prostatic tissue has a unique metabolic feature as it accumulates citrate as opposed to oxidizing it for use in the Krebs cycle. The net production in citrate is fostered through the build up of zinc at the highest concentration found in the body due to highly upregulated Zn transmembrane transporters, ZIP1. High levels of zinc inhibit *m-aconitase*, the oxidizing enzyme of citrate, thus leading to citrate buildup in the cells (13-15). Citrate and zinc are then excreted as a component of the seminal fluid.

However, a well-noted shift occurs within malignant prostate cells, which begin oxidizing citrate and no longer accumulate zinc due to downregulation of the ZIP1 transporter (13) The oxidation of citrate resumes the normal activation of the Krebs cycle. This is unique to prostate

cancers as most other cancers avoid the Krebs cycle, perhaps due to the cytotoxic effect of some metabolites produced. One theory for the reduction of zinc in malignant cells is that zinc can itself be cytotoxic, and as such, cancer cells attempt to decrease their zinc levels in order to survive. Altering these transporters does not allow the concentration of zinc to reach levels sufficient to inhibit *m-aconitase* (16). By reducing the zinc concentration, malignant cells are able to utilize the Krebs cycle more completely allowing for more efficient energy production while at the same time avoiding the toxicity of zinc. Zinc has been studied as a potential therapeutic target in an attempt to utilize this cytotoxic effect to fight malignant cells. This includes the potential of increasing zinc ingestion by those with disease or those at risk of developing the disease (17,18).

Lipid

Lipid utilization is key for continued growth and replication of tumor cells. So too, in prostate cancer malignant cells can utilize androgens to produce lipids or synthesize lipids *de novo* (19). Early in disease progression, the cancer cells tend to be more reliant on androgens to produce lipids. Once they can synthesize their own lipids the cells reach the stage of castration resistance and androgen deprivation no longer inhibits tumor proliferation (20). This is also a stage of more aggressive disease, where limited effective therapies exist. Some prostatic cancer lines have been shown to overexpress major components of fatty acid metabolism including fatty acid synthase (FASN), sterol regulatory element binding protein 1 (SREBP1), and stearoyl CoA desaturase (21).

The enzyme FASN functions to help synthesize long-chain fatty acids, which subsequently are used as a major source of energy for cells (22). FASN is upregulated by SREBP1. SREBP1 has been shown to be overexpressed in prostate cancer, as it is stimulated by epidermal growth factor and androgens. This increase in SREBP1 results in an increase in FASN in these cells (23). FASN upregulation is a common metabolic phenotype among many prostate cancer cell lines and is commonly used as a biomarker of disease. Furthermore, it has been argued that the increased FASN activity within prostate tissue marks the beginning of malignant disease. FASN may indeed be necessary to maintain growth of these lines as they increase lipid synthesis and create an alternative pathway to energy formation (24).

Stearoyl CoA desaturase is involved in the formation of monounsaturated fatty acids from larger saturated fatty acids (25) There has been evidence from animal models to show that regulation of stearoyl CoA desaturase has the potential to limit cancer growth.

Recent research has been done on how patient's obesity can alter their cellular metabolism (26,27) Notably obese patients have an increase in the availability of fatty acids useful for rapidly reproducing tumor cells. An interesting observation is that obesity has been linked not only to potential increase in prostate cancer incidence but also with a more aggressive cancer. As with much metabolic research, mechanistically the linkage is not yet fully understood (19). However, recent work in rodent models has shown that high fat diets can drive metastasis through modification of SREBP (28). This new information leads to a potential preventative measure in reducing aggressive prostate cancer incidence.

Androgen

Most cancerous cells within the prostate rely on androgens to multiply. The androgen receptor pathway has been found to alter the overall metabolism of the cell, including fatty acid metabolism, in addition to facilitation biosynthesis of many proteins needed for tumor growth (29). As such, androgen deprivation therapy has become a mainstay of early treatment. By inhibiting the downstream effects of androgen receptor activation, the progression of disease can be temporarily halted. In the elderly this may halt progression long enough that the disease may not interfere with life again. However, the cells eventually evolve to become unresponsive to androgen deprivation therapy. Multiple mechanisms can lead to treatment resistance. These include an upregulation of androgen receptors, an upregulation of androgen synthesis and the utilization of alternate routes of androgen receptor activation (30). At this point, tumors are referred to as "castration resistant" and the overall prognosis significantly worsens, as there are limited further treatment options (31).

Metabolism in aggressive prostate cancer

Lactate

Late stage prostate cancer cells begin using aerobic glycolysis. A byproduct of this process is lactate. Studies in models and in human subjects have shown that elevated lactate to pyruvate ratios are correlated with more aggressive tumors (32,33). This may be because these tumors have

begun utilizing aerobic glycolysis at a higher rate thus converting more pyruvate into lactate rather than breaking pyruvate down into the Krebs cycle (34). This ratio can be used clinically in magnetic resonance spectroscopic imaging studies to help determine the aggressiveness of disease.

Cells that rely on aerobic glycolysis face a problem however in that lactate is cytotoxic. To avoid lactate toxicity malignant cells have been shown to overexpress monocarboxylate transporters (MCTs) to reduce intracellular lactate levels (35). In theory cells that can handle the lactate burden the best, will be the most aggressive in nature as they are less limited by its toxic effect. This has been seen that more aggressive cancers have more MCT activity (32). As such these shuttles are a theoretical therapeutic target as to inhibit the MCTs may lead to increased cytotoxic effects within cancer cells.

PI3K/Akt/mTOR

The mTOR pathway has been reported to act as a key regulator of cancer cells energy metabolism through the fundamental role of Akt that stimulates aerobic glycolysis (36). Aberrant activation of the PI3K-Akt-mTOR pathway is implicated in prostate carcinogenesis. In addition, inactivation of both p53 and phosphatase and tensin homolog (PTEN) may promote tumor invasiveness via up-regulation of mTOR signaling, with a correlation with aggressive disease and poor survival in human prostate tumor. The serine/threonine kinase Akt is commonly activated in cancer cells, acting as an oncogene promoting cell survival. Frequently, Akt hyper-activation can indirectly result from amplification of the upstream Akt activator phosphatidylinositide-3-kinase (PI3K), or deletion of the PI3K inhibitor PTEN. Akt promotes the shift to aerobic glycolysis rendering cancer cells dependent on glucose consumption for growth and survival, contributing to a more aggressive cancer behavior (37). Several molecular mechanisms are implicated in Akt-dependent shift to aerobic glycolytic metabolism, including direct stimulation of glycolytic enzymes such as glucose transporters and hexokinase. In addition, activated Akt impairs the ability to induce fatty acid oxidation in response to glucose deprivation. The downstream effects of mTOR include the expression of glycolytic enzymes, including GLUT1, hexokinase 2 among others (37). mTOR directly stimulates the translational machinery by phosphorylating eIF4E binding proteins and ribosomal protein S6 kinases, and HIF-1α transcription factor enhancing expression levels of glycolytic proteins and genes (38). Targeted inhibition of PI3K/Akt/mTOR will likely be used in further treatment of aggressive prostate cancer.

PTEN

PTEN is a tumor suppressor, which functions to inhibit the activity of protein kinase B (PKB also known as Akt). The PKB signaling pathway promotes cell survival and proliferation as well as migration. PTEN promotes oxidative phosphorylation in addition to downregulating glycolysis (39). Downregulation of PTEN has been shown to lead to increased tumorigenesis. Decreased PTEN levels may correspond with increased aggressiveness of prostate cancer and is being evaluated as a potential biomarker of disease severity (40,41). As with many biomarkers of disease progression, PTEN will likely be used in the future in combination with a variety of other tumor markers including ETS-related gene (ERG) to assist in assessing prognoses. Despite the promising outlook of PTEN utilization, work still needs to be done to demonstrate the utility of using PTEN mutations to guide clinical decision-making (42).

Amino acids

Arginine

Arginine a non-essential amino acid involved in cell growth and protein synthesis. Arginine can also be converted to other key amino acids of proline and arginine. Nitric oxide (NO) can be formed from arginine by the enzyme NO synthase (43). NO has been implicated in cancer metabolic, however, the role of arginine derived NO in prostate cancer is as of yet not elucidated. However, arginine has been shown to aid in maintenance of malignant cell lines in prostate cancer. Studies have shown that arginine is needed to continue the growth of prostate cancer, despite the adequate knowledge of the exact biomechanism behind this. This has led to arginine deprivation therapy as a potential treatment regimen being tested in clinical trials (44).

Arginine can be synthesized from ornithine, a key component of the urea cycle. Ornithine carbamoyl transferase catalyses the reaction turning Ornithine and carbamoyl phosphate into citrulline. Citrulline is subsequently transformed into arginine by arginosuccinate synthase. Studies on prostate cancer *in vitro* have shown that these tumor cells produce lower amounts of ornithine carbamoyl transferase. These lines are sensitive to recombinant human arginase. Arginine deiminase can

deplete cellular stores of arginine and has been shown *in vitro* to kill tumor cells. Phase II clinical trials have been started using a combination of these two approaches (43,45).

Sarcosine

In recent years the utility of sarcosine, an n-methyl derivative of glycine, as a marker of prostate cancer has been described. Initially, there was a great amount of interest in sarcosine as a potential biomarker (4,46). Elevated levels of this amino acid derivative have been associated with progression of disease to a more aggressive phenotype. Sreekumar *et al.*'s paper shows, the removal of sarcosine dehydrogenase from benign prostate epithelial cells increases the concentration of sarcosine and increase cancer cell invasions while the removal of either dimethylglycine dehydrogenase or glycine N-methyltransferase in prostate cancer cells decreases cell invasions. This demonstrates that sarcosine metabolism plays a key-role in prostate cancer cell invasion and migration. Sreekumar's study suggests that sarcosine dehydrogenase and other enzymes in the sarcosine metabolism pathways could be potential therapeutic targets for prostate cancer (47). The excitement around this potential biomarker was further increased by the ease of quantifying amounts through urine analysis (47). This ease of identification represents a high clinical utility in identifying disease. However, this has yet to be proven, and work from Jentzmik *et al.* analyzing sarcosine level in 92 patients with prostate cancer draws a different conclusion. Despite showing an increase in levels of sarcosine in malignant samples, the levels of sarcosine were not associated with grade, stage, or recurrence of the tumors. As such they assert that sarcosine cannot be used as an indicator or biomarker for prostate cancer aggressiveness (48).

Vitamin E and selenium

An early attempt at using prostate metabolism as a therapy was seen in the SELECT trial. There was preliminary evidence that showed that higher levels of selenium and vitamin E may have had a chemoprotectant factor in the disease. It is currently hypothesized that selenium and vitamin E have strong antioxidant properties. These antioxidants in turn reduce oxidative stress, thereby lowering the number of cellular insults and decreasing the risk of tumorigenesis (49) The trial involved increasing patients intake of selenium and vitamin E through supplementation. However, this study was stopped early after there was found to be no chemoprotective benefit and perhaps increasing some cancer risk (50). This study underscores how difficult it is to not only discover metabolic differences of cancer cell lines but also how hard it is to predict the outcome of manipulating them.

Choline

Choline is the building block of phosphatidylcholine, which is a key component in cell membranes. In rapidly reproducing cell lines a higher amount of choline is needed. This concept has been utilized in cancer imaging. With 11C-choline PET scans being evaluated as potential ways to monitor disease progression (51,52). It has been shown that the amount of choline uptake in a tissue may correlate with disease aggressiveness; the more choline a sample takes in the more aggressive or high risk the disease (52). The mechanism by which choline is upregulated is as of yet elucidated. Currently 11C-choline scans are mainly utilized in detecting recurrent disease but the utility in primary detection is still being discussed (53).

Metabolic enzymes

Several metabolic enzymes, such as hexokinase 2, lactate dehydrogenase A and pyruvate dehydrogenase kinase 1, are direct targets of oncogenic transcription factors, such as MYC and hypoxia-inducible factor-1α in prostate cancer (54). Moreover, emerging evidence suggests that metabolites derived from altered metabolism influence oncogenic signaling pathways in a reciprocal manner, and that such interactions may be the basis for tumor progression and/or resistance to conventional chemotherapeutic approaches. Recently, it has been discovered that prostate cancer cells seem to preferentially depend on specific isoforms of glycolytic enzymes, prompting a search for isoform-specific inhibitors, which should increase drug specificity to cancer cells and avoid toxicity to normal cells (55). Key metabolic pathways and enzymes being investigated as potential targets include the muscle-specific isoform of hexokinase 2 and phosphofructokinase 2. Prostate tumor-specific expression of these isoforms has led to identification of isoform-specific inhibitors that have substantially suppressed tumor growth in preclinical studies and are being tested clinically (56).

Discussion

Prostate cancer as an entity represents an extensive disease burden on society, as it is the most non-cutaneous cancer diagnosed in men (57). The heterogeneity of the disease has

led to different treatment modalities based on aggressiveness of disease. As mentioned above there are metabolic markers that are relatively ubiquitous among these cancers. Recent research has been done into finding markers that may correlate to severity of disease prognosis. This field is still relatively young however it is expanding very quickly. While there may not yet be newly identified metabolic markers that can change clinical practice, there is evidence that this might soon be on the way. Whether it is through urine metabolites, markers in the blood, or new forms of imaging new modalities, using metabolomics may better stratify risk of disease severity and guide treatment. In addition to the diagnostic implications of understanding metabolism of tumor cell lines, this knowledge helps uncover potential therapeutic targets of disease.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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