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REVIEW ARTICLE

Prostate Cancer Tissue Biomarkers Associated with Tumor Microenvironment and Progression: Application of NMR Spectroscopy

Pradeep Kumar* *and Sujeet Kumar Mewar*

Department of NMR, AIIMS, New Delhi, India

***Corresponding author:** *Pradeep Kumar, Department of NMR, AIIMS, New Delhi-110029, India, Tel: +91-9873282071*

Abstract

In cancers of men, prostate cancer (PCa) is a prevalent malignancy. Finding biomarkers is important and useful for figuring out PCa incidence and prognosis. For males over 50, prostate cancer (PCa) is the most prevalent adenocarcinoma type of cancer diagnosis. PCa typically has a variety of clinical and pathological symptoms and is heterogeneous and multifocal. There is currently little knowledge about the molecular genetics of the progression mechanism behind this variability. The most effective method for examining unidentified metabolites in biological biomaterials is nuclear magnetic resonance (NMR) spectroscopy. Furthermore, metabolomics is a systems approach that aims to offer information on metabolic abnormalities associated with PCa by analyzing *in vitro* metabolic profiles. The most notable alterations in the microenvironments of prostate tissue with and without tumors are those involving some important metabolites such as citrate, amino acids, and phospholipids. This review includes the metabolomic research carried out in PCa tissues using NMR spectroscopy from the ongoing study of PCa biomarkers associated with the tumor microenvironment.

Keywords

Prostate cancer, Tumor microenvironment, NMR spectroscopy, Prostate tissue, Progression, Biomarkers

Introduction

Prostate cancer (PCa) is the most frequently diagnosed malignancy in men over the age of 50-years-old worldwide [1]. In its early stages, there are no clinical signs and the cancer grows slowly. The main risk factors for the development of cancer, such as age, race, and family history, are not well known in the pathogenesis of PCa. Furthermore, environmental, dietary, and way of life could affect genetics and trigger cancer processes [2]. Elevated levels of blood prostate-specific antigen (PSA) and abnormal digital rectal examination (DRE) are the marks of PCa screening and are tracked by transrectal ultrasonography (TRUS) guided prostate biopsy and grading system. Due to their low specificity and sensitivity, these approaches have some limits when it comes to diagnosing PCa. They can also yield false negative results, which can result in over diagnosis and overtreatment [3,4]. Due to the lack of a viable, sensitive, and specific tumor biomarker or markers, PCa is challenging to diagnose.

PCa start, growth, invasion, and metastasis are all influenced by several molecular processes. Even though the condition is common, little is known about the genetic changes that take place throughout this process. PCa predominantly affects the prostate glands of a peripheral zone (PZ), whereas benign prostatic hyperplasia (BPH) mostly originates in the transition zone (TZ) [4,5]. The last ten years have seen a notable decrease in PCa-related mortality due to the expanded and widespread use of PSA screening as well as modifications to treatment protocols. Nevertheless, PSA screening for PCa early detection is not without its limits. Prostatic intraepithelial neoplasia (PIN), BPH, prostatitis, and other non-malignant disorders of the prostate can all be associated with high PSA levels since the hormone is organ-specific rather than cancer-specific [4,5]. Therefore, serum PSA levels by themselves are unable to differentiate between adenocarcinoma and

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other benign prostate illnesses. The rise in incidence rates has also been attributed to several additional variables, including genetic variations, environmental factors, dietary changes, obesity, and the acceptance of PCa screening [4,5]. Although the specific origins of PCa remain unknown, aging, ethnicity, and inheritance are known to play significant roles in the onset and progression of malignancy. The most common risk factor is thought to be aging, with males between the ages of 60 and 70 being diagnosed in the majority of instances. The increased death rate is believed to be caused by late identification of PCa in advanced or metastasized stages as well as differences in resources for access to therapy [4,5].

Numerous investigations have demonstrated the role of the tumor microenvironment in the initiation, progression, invasion, and metastasis of cancer. Important components of the tumor microenvironment, infiltrating stromal and immune cells have been demonstrated to have a major impact on the development of malignancy [6]. There is evidence that the development of cancer and the determination of tissues for metastasis are mediated by interactions between tumor cells and stroma. PCa etiology and development are primarily driven by the androgen receptor (AR), which is expressed by the stromal cells in PCa. Investigating the causative impact of gene expressions on the prognosis of PCa patients in the tumor microenvironment remains challenging [6]. In the review, we addressed the metabolites found by NMR spectroscopy in prostate tissue derived from the tumor microenvironment of PCa.

One characteristic of solid tumors that has been identified is metabolic reprogramming. Tumour development and progression are fuelled by malignant alteration of the tumor bioenergetics. Consequently, the changed metabolism during tumor growth may present potential for innovative treatment techniques, especially in advanced PCa stages, even if the alterations in metabolism are not fully understood [7].

Metabolomics profiling using NMR continually in cancer biology including PCa is a novel and active field. Finding the unique biomarker(s) for diagnosis and identifying the collection of important metabolites and their metabolic pathways to get a deeper comprehension of the pathophysiology of the diseases are the goals of metabolomics in cancer studies [8-10]. Typically, metabolomics involves a tissue, cell, or organ and profiling every molecule (or a subset) in that biofluid (blood and urine). Prostate tissue from PCa patients has been the subject of significant NMR-based metabolomics investigations related to tumor microenvironment and development [8-10]. A characteristic of PCa is altered metabolism, which can regulate several malignant characteristics and promote carcinogenesis. Through proliferation and metabolic differentiation, metabolite targeting and metabolism modification play a role in carcinogenesis. This review includes a few current NMR-based metabolomics investigations that have been conducted on PCa.

Pathology of Prostate Cancer and Progression

PCa typically has a variety of clinical and pathological symptoms and is heterogeneous and multifocal. There is currently little knowledge about the molecular genetics of the progression mechanism behind this variability. In addition to the involvement of numerous genes in pathogenesis, other variables including nutrition, inflammation, and environmental conditions also play a role in the complex molecular pathophysiology of PCa. PCa is the most common type of cancer in men and contributes significantly to the global disease burden [11].

The pathophysiology of PCa is a field of active research. When a benign cell transforms into a cancerous one, several pathological changes take place. Many of the processes of pathogenesis and carcinogenesis remain poorly understood, necessitating extensive study in the field of cancer. Cuboidal to secretory epithelial cells with a junction and layer of basal and neuroendocrine cells make up the epithelium cells of the human prostate gland [11]. The human urethra is reached via the duct and the luminal area where the glandular acini that make up the epithelial cells secrete. A fibromuscular stroma is located on the basal lamina's opposing side. Immune cells, endothelial cells, and nerve fibers connected to the ganglia are additional essential cells in the stroma compartment [12]. These modifications may be linked to modified androgen and hormonal activity as well as inflammatory response strategies that result in either an unremitting trophic impact on the gland or chronic inflammation, even though the precise mechanisms behind these changes are not yet known. When combined with the precarious requirement for androgen action to regulate prostate pathology and results in a change in biochemistry from differentiated male reproductive function to chronic wound repair, it is possible that repeated epithelial infractions persisted throughout the aging process [12]. It suggests that various PCa, which share reactive stroma and irritation, are encouraged by the repair state pathology. It has been proposed that impatience and PCa are associated, and these changes can be detected by the development of significant reactive stroma biomarker(s) in the stromal segment. PCa is preceded by a premalignant disease called prostatic intraepithelial neoplasia (PIN). It used to be identified as dysplasia [12,13]. There are two grades of PINs: Low grade and high grade. Because it is challenging to differentiate low-grade PIN from benign prostate and because these individuals do not have an increased risk of developing cancer upon later biopsy, low-grade PIN is not reported in the present method. After receiving a high-grade PIN (HGPIN) diagnosis,

a patient had another biopsy. It's unclear how long it takes for PCa to start developing when HGPIN lesions are diagnosed [13]. According to a few additional studies, people with HGPIN had a about 26% chance of developing cancer throughout their follow-up. To identify the PIN, a needle prostate biopsy is carried out. It consists of up of large acini, or ducts, lined with cells that are unusual cytologically. PIN is cytologically similar to PCa. A pathological state of diagnostic uncertainty is atypical small acinar proliferation (ASAP). Concurrent or subsequent PCa requires repeat biopsy even if it is not a cancerous condition [13].

Physiology and Biochemistry of Prostate Cancer

Oxidative phosphorylation is crucial in many malignancies, even if the Warburg effect, the Krebs cycle, and the TCA cycle are important in malignant transform cells [14]. Accordingly, Mark proposes that elevated citrate (Cit) oxidation is a crucial metabolic signature in PCa that sustains the elevated cellular energy needed for carcinogenesis [14]. Prostatic epithelial cells play a crucial role in producing spermine, PSA, and citrate, the main ingredients of human prostatic fluid. In line with other human bodily organs, regular prostate gland cells produce a perfectly high amount of Cit. Prostate metabolism strongly positively discriminates Cit production over Cit consumption, which shapes the PZ epithelium to choose standard cells, among other diverse cells in the organism [15,16]. Cells often break down Cit in the process of producing aerobic ATP, with Cit being oxidized via the TCA cycle as a gauge of the intermediate metabolism of glucose (Glc). However, cells proliferate and release Cit. m-aconitase, also known as mitochondrial aconitase, is the enzyme that catalyzes the oxidation of Cit. Higher intracellular concentrations of zinc (Zn) in epithelial cells cause m-aconitase to become reluctant, which is crucial for Cit accretion. Neoplastic transforming of epithelial cells results in broad-spectrum metabolic alterations [15,16]. Of the most significant alterations, Cit oxidation is distinct because cancerous cells are unable to accumulate zinc and, in the absence of elevated zinc levels, m-aconitase is not completely inhibited, allowing it to catalyze Cit. When prostate cells undergo malignant transformation, oxidized Cit is produced in greater amounts by epithelial cells, leading to the creation of more competent energy [15,16]. Increased lipid production requires intercellular signaling and malignant cell growth. Because it is a precursor to cholesterogenesis and lipogenesis and can be created via Cit transformation in the cytoplasm, acetyl-CoA is a crucial step in the modulation of metabolic pathways [17]. Additionally, glutamine (Gln) plays a crucial role in lipogenesis repair and provides accessible intermediates for Cit cycle-wide glutaminolysis [17]. Figure 1 depicts a basic depiction along with a few significant metabolites linked to the malignant transformation of prostate epithelial cells.

NMR-Based Metabolomic Profiling of Prostate Tissue Associated with Tumor Microenvironments

Because NMR spectroscopy is a non-destructive, quantitative, and repeatable method, and because

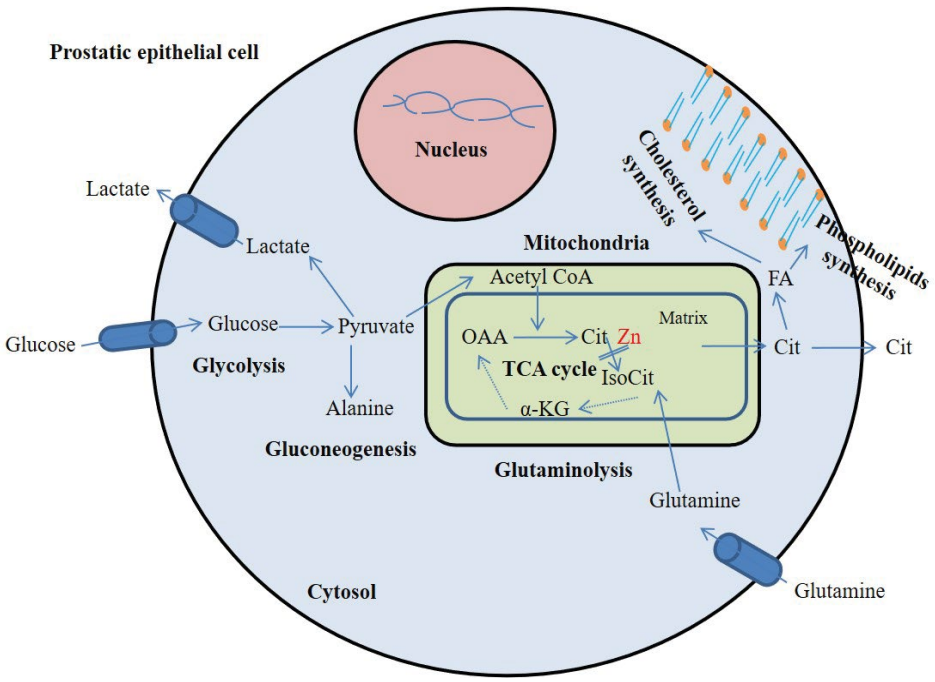

Figure 1: Schematic representation of the most significantly altered metabolic pathways in Prostate epithelial cells.
TCA Cycle: Tricarboxylic Acid Cycle; OAA: Oxaloacetate; Cit: Citrate; Iso-Cit: Iso-citrate; α-KG: alfa-Ketoglutarate; FA: Fatty Acids.

the spectra offer exceptional biochemical information, it has been extensively utilized for metabolic profiling [18,19]. Compared to ^{31}P-NMR and other methods, ^{1}H-NMR is more commonly utilized for the metabolic profiling of biological materials. Furthermore, two-dimensional (2D) studies are used, which primarily aid in the resonance assignment [18,19]. Several techniques for NMR-based metabolic profiling during prostate tissue metabolite extraction and different NMR steps of metabolic profiling have been reported in several PCa publications [8-10]. A simple explanation of the various NMR experiment stages for discovered metabolites in PCa as well as NMR-based metabolic profiling of PCa tissue are given in Figure 2.

The article focuses on the reported metabolites from the most recent study and NMR-based metabolic profiling of patients with PCa in prostate tissue [8]. Using a ^{1}H NMR-based metabolomics technique, a recent study published metabolic profiles of matched tissue, blood, and urine samples from the same individuals [8]. They discovered several key metabolites that underwent substantial changes at various stages of PCa, such as castration-resistant PCa, benign prostatic hyperplasia, early PCa, advanced PCa, and metastatic PCa. It was discovered that, in contrast to serum and urine samples, alterations in metabolic phenotypes that occur as PCa progresses appear stronger in tissue samples [8]. Here, they found several significant abnormalities in metabolism, including elevated trends of formate and uridine and reduced trends of citrate, creatinine, acetate, leucine, valine, glycine, lysine, histidine, glutamine, and choline. These metabolites are mostly associated with the metabolism of uridine, energy, amino acids, choline, and fatty acids [8]. These studies additionally found a positive relationship between serum and urine amino acid metabolism and energy metabolism in tumor tissues. Patients with CRPC also had an unusual metabolic profile, particularly reduced blood amino acid metabolism. The describes metabolic abnormalities in tissue and biofluid samples as PCa advances and offers prospective biomarkers for the diagnosis and treatment of PCa [8].

It is crucial to carry out more research to clarify how different PCa subtypes differ in their study reported for energy and anabolic chemicals to generate more potent treatments and diagnostic tools [9]. Here, they conducted a thorough examination of prostate tissue samples to identify changes in metabolism that occur both during the onset and advancement of PCa, as well as between positive and negative TMPRSS2-ERG rearrangement of PCa subtypes [9]. This work described a comprehensive metabolomics analysis using high-resolution magic angle spinning nuclear magnetic resonance on prostate tissue samples that are non-destructive. Samples are subsequently moderately extracted while maintaining tissue shape for

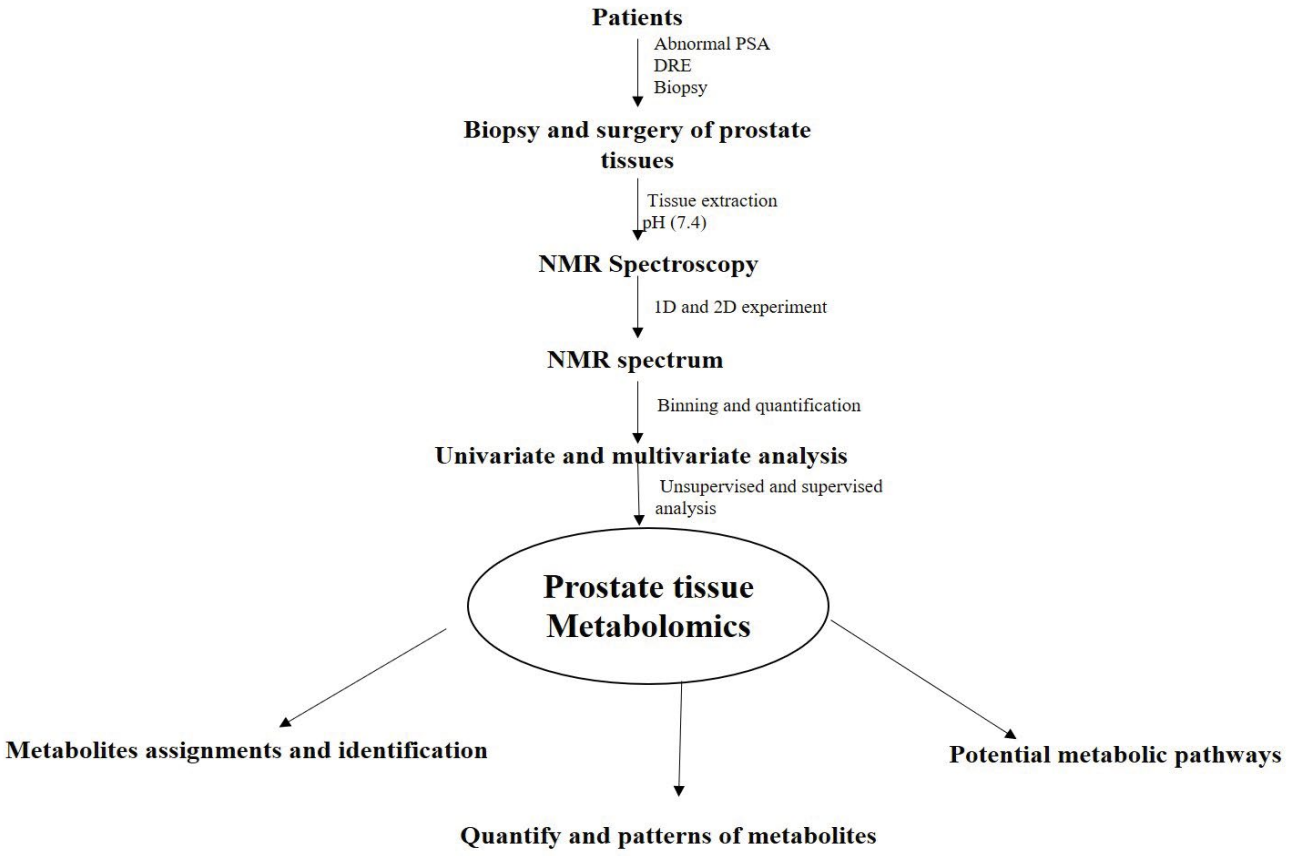

Figure 2: Simple presentation of NMR-based metabolic profiling of prostate tissue and different NMR experiment steps for identified metabolites in PCa.

histological characterization. Using both ^{1}H and ^{31}P NMR spectroscopy profilin, metabolites from prostate tissue extracts and identified [9]. Chemometric methods are used to analyze these metabolomics profiles, and the results are further verified using proteome data from an additional sample cohort. The identified metabolite patterns demonstrated significant variations between benign tissue and PCa samples, as well as between samples with high and low Gleason scores. They discovered that the metabolites α-glucose, arginine, succinate/malate, phosphatidylcholine, sphingomyelin, and nicotinamide adenine dinucleotide (NAD+) are adequate to distinguish between high and low Gleason scores as well as between benign and cancerous tissue [9]. The research revealed that many acylcarnitines are found among the elevated metabolites in ERG-positive PCa, together with decreasing levels of proteins involved in β-oxidation. These imply that in ERG-positive tumors, acyl-CoA oxidation is impaired. Furthermore, purine catabolism-related metabolites and proteins were found in greater quantities in the ERG-positive group, which may imply increase oxidative stress as well as DNA damage [9].

Furthermore, another study reported that using the same PCa tissue sample, the reactive stroma content could be used to find the genes and metabolites that have been expressed differently [10]. Histopathology from recently frozen prostate tissue samples collected from patients with PCa subsequent prostatectomy is used to describe cases of reactive stroma. Magic angle spinning magnetic resonance spectroscopy with high resolution is used to analyze a portion of the samples for metabolic conditions. Additionally, they indicated that biochemical recurrence is used as an endpoint to determine recurrence-free survival in patients who have had clinical follow-ups for at least five years [10]. The Gene expression investigation and multivariate analysis of metabolomics have been utilized and compared to low and high reactive stroma content. In patients with PCa, uniform after monitoring for the grade group impact, a high reactive stroma content is related to and associated with biochemical recurrence. Metabolite and immune activities are clinically significantly altered in prostate tissue samples with high reactive stroma attention [10]. They found that among the clinically significant metabolites detected in PCa samples are citrate, spermine, taurine, scylla-inositol, and leucine. Additional validation of these findings is essential to identify novel biomarkers and therapeutic targets associated with immune systems and extracellular matrix (ECM) in PCa. They noted that the association they found between high reactive stroma grade and biochemical recurrence provides additional support for the clinical integration of this histological evaluation of the PCa [10].

Table 1 lists some prominent studies that used metabolic profiling based on NMR spectroscopy to look into altered metabolites in prostate tissue associated with TME. To better understand tumor microenvironments and diseases, further tissue-based metabolic profiling of PCa is needed to find metabolites and metabolite patterns for discriminating between tumor and non-tumor regions.

Conclusion

Reprogramming the cellular metabolism provides the high energy needs of rapidly multiplying tumor cells. In this review study, we concentrated on metabolic changes in the onset and progression of prostate gland cancer. In contrast to most solid tumors, the primary energy sources in early PCa are amino acid absorption and glucose uptake. On the other together, malignant transport is propelled by phospholipid metabolism. It's amazing how important lipid metabolism is for PCa at every stage. There has been minimal research on the metabolic interaction between epithelial cells prostate gland and TME, despite the reality that the metabolic reprogramming in PCa has been thoroughly

Table 1: List of significantly altered metabolites in prostate tissue associated with tumor TME using NMR spectroscopy-based metabolic profiling.

Tissue samples (Prostate tumor tissue)	NMR methods	Significant Altered metabolites in prostate tissue associated with TME	References
Low RSG (n = 58) and high RSG (n = 27)	^{1}H- NMR and ^{31}P-NMR	α-Glucose, NAD+, Arginine, Succinate/Malate Lysophosphatidylcholine, Phosphatidylethanolamine Sphingomyelin	[9]
PCa Patients (n = 16) Benign (n = 59)	^{1}H-NMR	Citrate and spermine taurine, scyllo-inositol and leucine	[10]
Patients with BPH (n = 18), EPC (n = 16), APC (n = 11), MPC (n = 23), and CRPC (n = 8)	^{1}H-NMR	Citrate, creatinine, acetate, leucine, valine, glycine, lysine, histidine, glutamine choline uridine, and formate.	[8]

NAD+: Nicotinamide Adenine Dinucleotide; TME: Tumor Microenvironment; RSG: Reactive Stromal Grading; BPH: Benign Prostatic Hyperplasia; EPC: Early PCa; APC: Advanced PCa; MPC: Metastatic PCa; CRPC: Castration-Resistant PCa

elucidated. This lack of evidence may also account for the majority of clinical studies' failure to demonstrate efficacy compared to standard treatments. However, considering that different stages of PCa seem to have different metabolic properties, the metabolism promises to offer a unique opportunity for the creation of personalized novel therapeutic approaches that will complement current medications.

Declarations

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All of the above authors have seen and approved the manuscript.

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