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Omics sciences and precision medicine in prostate cancer

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Abstract

In the last decade, Prostate Cancer (PCa) has emerged as the second most prevalent and serious medical condition, and is considered one of the leading factors contributing to global mortality rates. Several factors (genetic as well as environmental) contribute to its development and seriousness. Since the disease is usually asymptomatic at early stages, it is typically misdiagnosed or over-diagnosed by the diagnostic procedures currently in use, leading to improper treatment. Effective biomarkers and diagnostic techniques are desperately needed in clinical settings for better management of PCa patients. Studies integrating omics sciences have shown that the accuracy and dependability of diagnostic and prognostic evaluations have increased because of the use of omics data; also, the treatment plans using omics can be facilitated by personalized medicine.

The present review emphasizes innovative multi-omics methodologies, encompassing proteomics, genomics, microbiomics, metabolomics, and transcriptomics, with the aim of comprehending the molecular alterations that trigger and contribute to PCa. The review shows how early genomic and transcriptomic research has made it possible to identify PCa-related genes that are controlled by tumor-relevant signaling pathways. Proteomic and metabolomic analyses have recently been integrated, advancing our understanding of the complex mechanisms at play, the multiple levels of regulation, and how they interact. By applying the omics approach, new vulnerabilities may be discovered, and customized treatments with improved efficacy will soon be accessible. ***Clin Ter 2023; 174 Suppl. 2 (6):95-103 doi: 10.7417/CT.2023.2476***

Key word: *prostate cancer, omics sciences, genetics, transcriptomics, metabolomics, precision medicine*

Introduction

Prostate Cancer (PCa) is an important medical concern that has a considerable impact on the majority of men population—ranking as the second most prevalent form of malignancy in males (after lung cancer)—and is included in the top five leading causes of mortality globally. In Europe, PCa constitutes approximately 11% of the total male cancers (1), and in the European Union it is responsible for 9% of all cancer-related mortalities in men (2). Risk factors that have been scientifically proven to exist include advanced age, ethnicity, genetics, and family history (3-5). Aside from obesity and physical inactivity, the factors that can contribute to various health conditions for PCa include infections, inflammation, environmental exposures, diet, hyperglycemia, and ionizing radiation (4, 6-10). The initial phases of PCa often exhibit a gradual progression and absence of symptoms, thereby rendering therapy unnecessary. A further progression of the condition may manifest as urinary incontinence and lumbar discomfort (11).

The currently available PCa screening and therapy approaches are invasive and expensive, and frequently result in misdiagnosis or overdiagnosis of the condition; moreover, cancer relapse is quite common. Due to all these associated limitations with screening, increasing incidence rate, and all the risk factors contributing to it, an effective, accurate, non-invasive, and relatively cheaper PCa diagnostic and therapeutic strategy is required. Therefore, the objective of this study is to integrate multi-omics methodologies to better comprehend biomarker discovery and to speed up the adoption of precision oncology in PCa. This review summarizes recent research and highlights some studies that have applied multi-omics to PCa in unique and groundbreaking ways.

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Prostate Cancer Diagnosis and Therapy

Prostate Specific Antigen (PSA) tests, imaging studies, and prostate tissue biopsies are the mainstays of standard PCa diagnostic techniques (12). The efficacy of PSA testing is a subject of debate, owing to the occurrence of false positive results, which may lead to excess diagnosis and therapy of low-risk groups PCa with limited benefits (13). Ionizing radiation exposure during imaging tests can be expensive as well as harmful to health. Although CT scans are more expensive, they are known to have limited efficacy in identifying metastatic tumors or relapses of PCa in males with low levels of PSA. In the scientific field of therapeutics, the confinement of cancer to the prostate gland is classified as localized and has the potential for effective treatment. Radical prostatectomy, radiation, and surveillance are available as management options, however, there is little data to assess the merits of each strategy (14). Also, each approach has its own drawbacks, because cancer relapse is frequently observed in the case of targeted therapy and these methods are also intrusive, painful, and expensive.

PCa treatment options are currently limited to selective therapeutic drugs, including galeterone, abiraterone, and seviteronel, which are currently undergoing development. The present study evaluated the association and efficacy of Morusflavone flavonoid derived from Morus alba L., with CYP17A1. The FDA-approved CYP17A1 inhibitor functions by suppressing androgen production. CYP17A1 inhibition represents a significant therapeutic objective for the treatment of PCa. The results of a molecular dynamics simulation study suggest that morusflavone is a promising therapeutic target for PCa, since it is more stable than abiraterone and interacts with CYP17A1. There is a lack of data about the use of powerful naturally occurring anticancer chemicals like vinca alkaloids in the treatment of PCa (15).

Multi-Omic Approaches in Prostate Cancer Diagnosis and Management

The ineffectiveness of conventional approaches prompted researchers to come up with efficient and cutting-edge solutions to the present problems with PCa diagnosis and treatment. The advent of omics technology has led to unique initiatives aimed at characterizing the molecular alterations that underlie the onset and progression of various intricate medical conditions such as cancer (16). The field of cancer biology has increasingly relied on the acquisition and synthesis of information obtained from diverse sources, particularly with the advent of sequencing technology. One of the main difficulties related with the use of omics sciences in the diagnostic and therapeutic sectors is tumor heterogeneity, which makes it challenging to develop biomarkers that precisely reflect the characteristics of the entire tumor. Furthermore, data integration from multi-omics platforms is required for collecting and analyzing enough tissue samples.

Genomics, transcriptomics, proteomics, and metabolomics approaches can all be utilized today to thoroughly analyze the underlying mechanisms and to understand the numerous variations taking place (16). Particularly for advanced PCa, molecularly driven therapeutic targets are anticipated to enhance intervention as part of customized treatment plans based on novel, more targeted medicines, directed by omics-based biomarkers (17). Light has been shed on PCa etiology by genome-wide association studies, which have identified numerous predisposition loci and highlighted the importance of genetic variations (18). On the examination of PCa gene drivers, disease subgroups are identified, and therapeutic alternatives are created for precision medicine techniques.

Given the high correlation among the expression of many genes, the transcriptomics approach is commonly employed to assess the regulation of genes and to identify tumor subtypes (19). When mRNA profile of PCa were constructed, non-coding RNAs (ncRNAs) in the growth of cancer were discovered to be enhanced after radiotherapy, and the presence of this particular factor may indicate an adverse prognosis for the overall survival of individuals diagnosed with PCa (20).

Proteomics, being an omics approach, has been extensively employed in various research endeavors aimed at identifying biomarkers for PCa. This is due to its ability to directly reflect cellular activity and identify dysregulations in a variety of biological constituents (21). Proteomic alterations have been linked to metabolic activity, DNA repair, cell cycle regulation, and proteasomal degradation. Shina et al.'s study analyzed various Omics methodologies and assessed the precision of each biomarker. They discovered that proteomic characteristics were much more relevant than genomic, epigenomic, or transcriptomic features for predicting biochemical relapse (22). In a study conducted by Maria et al., the PNT1A, DU145, PC3, and LNCaP prostate cell lines were used to identify potential protein candidates associated with the progression of PCa (23). Tonry conducted a comprehensive assessment of the application of proteomics in the identification and personalized management of PCa (24).

Metabolomics has provided additional support in the characterization of the distinct metabolic profile associated with the progression of PCa and in the identification of metabolic alterations, which might be helpful as clinical biomarkers. To achieve this objective, several metabolomics studies have been conducted on PCa samples in recent times. Many technological advancements are currently accessible for the purpose of identifying and quantifying diverse metabolites in cells, tissues, or biofluids (25-27). Analytical procedures are based on mass spectrometry (MS) and nuclear magnetic resonance (NMR). The metabolomes from healthy and cancerous prostate tissues differ in lipid, nucleotide, Tricarboxylic acid (TCA) cycle, polyamine, and hexoamine production (28, 29). PCa is known to have elevated de novo lipogenesis (30), and cell lines produced from PCa metastases have upregulated levels of various lipid types. Urine metabolomics is a prompt and precise approach for the identification of diagnostic biomarkers for PCa, as well as predictive response biomarkers. The utilization of a metabolic signature has been proposed as a means of prognosticating diagnosis (31). According to independent research (25, 32), several metabolites—including a great number of those associated with the synthesis of energy, TCA cycle, and the metabolism of amino acids—are changed in urine. The omics approaches that are being employed in diagnostics and therapeutics of PCa are described in the following paragraphs.

Genetics of Prostate Cancer

Among all PCa risk factors, the patient's genetic makeup is considered the most significant one: according to reports, a person has 50% chances of developing PCa if an individual in their family has this disease (33). . To confirm the hereditary link of PCa, scientists have conducted many studies in which they have used twin, case-control, and family groups; the results showed that specific genetic mutations in people are increasing the risk of developing this disease (34). Different genes linked to PCa are listed in **Table 1**.

BRCA1, BRCA2, and ATM are the DNA repair genes, which are present in 5.5% of the men with PCa (35). Point mutations in the DNA sequences, such as single nucleotide polymorphisms and somatic copy number alterations, are relevant to the development of PCa because they silence the transcriptional activation of tumor suppressor genes, thus making the oncogenes functional (36, 37). The mutations during DNA replication in the nucleus pass on to the next generation, leading to the development of PCa due to the uncontrolled growth of cells with these mutations (38).

Genomics of Prostate Cancer

Almost all primary and metastatic PCa patients have been linked to mutations in the somatic genes (such as AR, WNT, PI3K-PTEN) and in the cell cycle signaling and DNA repair pathways. Different large genome studies have been conducted to find the association between metastatic castration-resistant (mCRPC) and PCa, which can be because of mutations in the genes, gene fusion, copy number variations of DNA, and rearrangements of genes (39, 40). In 1948, when cell free DNA (cfDNA, or the portion of circulating nucleic acid) was discovered in the blood (41). By conducting different research on PCa patients, scientists found out that, compared to healthy people, they had a higher number of longer cfDNA fragments, which increased concurrently with the stage and severity of the disease (42).

Transcriptomic of Prostate Cancer

The total number of RNA transcripts in an organism can be identified by transcriptomic studies. With the help of this, a total of 11 RNAs have been studied: among them, the mRNA, being translated into a protein after being transcribed from DNA, is the most concerned in cancer (43). The specific tumor type can be identified with the help of transcriptomic studies by measuring the expression of the genes: a higher gene expression means that they are closely related to each other and also are linked to tumor (19).

PCa progression can be predicted by the change in the mRNA level. This change will help in determining the difference between the normal and the metastatic state of PCa. Nine different stage-specific candidate genes linking to PCa progression are listed: *GSTP1*, *TP63*, *MYC*, *CENPA*, *EZH2*, *PIK3CB*, *HEATR5B*, *DDC*, and *GABPB1-AS1* (44, 45). The detailed transcriptome studies not only focus on the mRNA, but also include non-coding RNAs and their subtypes. The next generation sequencing (NGS) technique is used to study the transcriptomic profile of cells or tissues in detail (46-49).

The RNA biomarkers of PCa are listed in Table 2.

Table 1. List of genes linked to PCa and related syndromes.

Gene	OMIM of the Gene	Gene Location	PCa Histologic Characteristics	Inheritance	OMIM of the Pathology	Related Pathologies
MAD1L1	602686	7p22.3	PCa, somatic	.	176807	- Mosaic variegated aneuploidy syndrome 7, with inflammation and tumor predisposition; - Lymphoma, B-cell, somatic.
PTEN	602053	10q23.31	PCa, somatic	.	176807	- Macrocephaly/autism syndrome; - Cowden syndrome 1; - Meningioma Lhermitte-Duclos disease; - Glioma susceptibility 2.
KLF6	602053	10p15.2	PCa, somatic	.	176807	- Gastric cancer, somatic.
MXI1	600020	10q25.2	PCa, somatic	.	176807	- Neurofibrosarcoma, somatic.
BRCA2	600185	13q13.1	PCa	AD, SMu	176807	- Fanconi anemia, complementation group D1; - Glioblastoma 3; - Pancreatic cancer 2; - Breast cancer, male, susceptibility to; - Breast-ovarian cancer, familial, 2; - Medulloblastoma.
ZFHX3	104155	16q22.2-q22.3	PCa, somatic	.	176807	- Prostate cancer, somatic
CHEK2	604373	22q12.1	PCa, familial, s usceptibility to	AD, SMu	176807	- Li-Fraumeni syndrome 2; - Osteosarcoma, somatic; - Breast cancer, susceptibility to; - Colorectal cancer, susceptibility to.
AR	313700	Xq12	PCa, susceptibility to	AD, SMu	176807	- Androgen insensitivity; - Androgen insensitivity, partial, with or without breast cancer; - Hypospadias 1, X-linked; - Spinal and bulbar muscular atrophy of Kennedy.

Table 2. List of potential biomarkers for PCa, including long non-coding RNAs, circular RNAs, and microRNAs.

lncRNAs	Expression	Sample	Potential Biomarker	References
PCA3	Increased	Tissue/urine	Diagnostic/therapeutic	(50-54)
MALAT1	Increased	Tissue/plasma	Diagnostic/predictive	(55-59)
SChLAP1	Increased	Tissue/plasma/urine	Diagnostic/prognostic	(60-62)
FR0348383	Increased	Tissue/urine	Diagnostic	(63, 64)
PCAT1	Increased	Cell lines/tissues	Therapeutic	(65)
CCAT2	Increased	Tissues	Prognostic	(66)
CTBP1-AS	Increased	Tissues	Prognostic	(67)
DRAIC	Decreased	Cell lines	Prognostic	(68)
HCG11	Decreased	Tissues	Prognostic	(69)
LINC01296	Increased	Cell lines/tissues	Prognostic	(70)
LincRNA-p21	Decreased	Cell lines	Prognostic	(71)
LncRNA-ATB	Increased	Tissues	Prognostic	(72)
LOC440040	Increased	Cell lines/tissues	Prognostic	(73)
NEAT1	Increased	Cell lines/tissues	Prognostic	(74)
PCAT14	Increased (early)/ decreased (late)	Tissues	Prognostic	(75)
PCGEM1	Increased	Tissues	Prognostic	(76, 77)
TRPM2-AS	Increased	Tissues	Prognostic	(78)
UCA1	Increased	Tissues	Prognostic	(79)
circRNA				
circMYLK	Increased	Tissue	Diagnostic/therapeutic	(80)
miRNA				
miR-96	Increased	Tissue	.	(81)
miR-96-5p, miR-183-5p	Increased	Tissue	.	(82)
miR-145-5p, miR-221-5p	Decreased	Tissue	.	(82)
miR-221	Decreased	Tissue	.	(83)
miR-21, miR-22, miR-141	Increased	Plasma	.	(84)
miR-141, miR-375	Increased	Serum, tissue	.	(85)
miR-20a, miR-21, miR-145, miR-221	Increased	Plasma	.	(86)
miR-107, miR-574-3p	Increased	Urine	.	(87)
miR-200b, miR-200c	Increased	Plasma	.	(88)

Metabolomics

The primary objective of metabolic analysis is to quantify and characterize a maximum number of metabolites, with the ideal outcome being a comprehensive depiction of the metabolome. Biochemical pathway-related metabolic alterations can help uncover complex disease reasons. All of this information might lead to the identification of novel biomarkers for disease within current diagnostic procedures (89).

Proteomics and Biomarkers

According to recent investigations on cancer, only 10% to 20% of changes in proteome analyses may be attributed to changes in the transcriptome (90). Proteomics has been used in PCa biomarker research because it provides an instant analysis of the functioning of cells and reveals alterations in the most treatable biological components (21). By integrating the genomic data with the proteome of the tissue, it is possible to discover biomarkers and locate potential therapeutic targets. Furthermore, in situ histopathology permits researchers to further investigate the genetic basis of cancer initiation and progression. By using 2-Dimensional differential gel electrophoresis (2D-DGE) and western blotting, many protein indicators were identified as the PCa biomarkers, like UBE2N, Ser/tre-protein phosphatase PP1β (PPP1CB), and PSMB6 (91). SMARCA4 deletion impacts the chromatin accessibility and thus the gene regulation of a subset of AR genes, as well as CRPC development and dissemination (92).

Proteomic comparisons of PCa normal and cancerous tissue are also used to learn about the carcinogenic process. Interindividual differences can be ruled out by analyzing the prostate tissue with distinct histological patterns. PCa tumor stroma has more calcium-binding, intercellular interstitial, and smooth muscle contraction proteins than normal stroma (93). A significant contributor to the overtreatment of men with PCa is PSA, which is the best-known biomarker for PCa diagnosis and also a frequently employed biological indicator in investigating cancer (94).

Proteomics can identify biomarkers and therapeutic targets in health and disease systems biology. Precision medicine and proteomics help precision oncology in analyzing complicated carcinogenic pathways and targeted therapies, finding novel biomarkers for screening and detection, and evaluating therapy effectiveness and toxic effects (95).

Some of the major proteomics biomarkers responsible for renal cell carcinoma are mentioned in **Table 3**.

Table 3. List of Proteomics biomarkers linked to PCa.

Proteomics Biomarkers	Protein Family	Expression status	Assays for identification	References
PPP1CB	Metabolic proteins Plasma proteins	Decreased	2D-DGE MS	(91)
Ubiquitin-conjugating enzyme E2N	Cancer-related genes Enzymes Metabolic proteins Plasma proteins	Increased	2D-DGE MS	(91)
Coatomer protein complex, subunitα	Disease-related genes Metabolic proteins Plasma proteins	Increased	Immunohistochemistry (IHC) MS	(96)
Vinculin	Disease-related genes Plasma proteins	Increased	2D-DGE MS	(97)
Transthyretin	Cancer-related genes Human disease-related genes Plasma proteins	Increased	MALDI-TOF MS, MS, 2D-DGE, IHC	(98)
MethylcrotonoylCoenzyme A carboxylase 2 (beta)	Disease-related genes Enzymes Human disease-related genes Metabolic proteins Potential drug targets	Increased	MALDI-TOF MS 2D-DGE, IHC, Western Blotting	(99)
Periostin	Cancer-related genes Plasma proteins	Increased	2D LC-MS/MS and iTRAQ	(100)

Lipid omics and biomarkers

Disease research recently adopted lipidomics. The identification of different lipid biomarkers for particular health issues is important, because many diseases cause unique and distinctive alterations in the lipid compounds of bodily fluids or tissues before clinical symptoms appear (101). The vast array of lipids presents a significant challenge in the research and development of analytical techniques for lipidomics. MS, particularly in conjunction with chromatographic separation methods, is a highly prevalent approach in the field of lipidomics. The quantitative examination of lipids in biologic specimens using MS has yielded copious data that can be used for the clinical assessments of various diseases (102). The implementation of the lipidomics approach has gained significant traction in cancer research due to its ability to accurately delineate the lipid structures and compositions present in specific cells or organisms (103). Different mitogens—such as lysophospholipds, lysophosphatidic acids, phospholipids, and phosphatidic—are responsible for PCa. Lipid kinases, G protein-coupled receptors, and small G proteins are major factors responsible for the complications in different cellular signaling pathways and cytoskeletal rearrangements (104).

In the case of lipidomics, a lipid profile and metabolic pathway can be constructed. This procedure involves the extraction of lipids from tissues and cells, followed by lipid analysis, which eventually contributes to the construction of the lipid profile, as well as its analysis and subsequent pathway analysis (103). The study conducted by Zhou X. et al. aimed to explore the potential diagnostic and prognostic significance of lysophosphatidylcholine transferase 1 (LPCAT1) in prostate tumors by using IHC on tissue microarray slides. The study examined the association between LPCAT1 expression and cancer advancement. The pivotal function of LPCAT1 in the modification of PLs and its upregulation in various carcinomas (such as colorectal and prostate) in contrast to healthy mucosa had previously been established (105, 106).

Microbiomics and Biomarkers

Current research indicates that changes in the composition of microbiota, known as dysbiosis, may have a significant impact on the onset, progression, and outlook of PCa. The microbiome, which encompasses the entirety of microorganisms and their genetic material residing on and within the body, is acknowledged as a significant factor in the identification of various cancer types. Various extensively researched human microbiomes, consisting primarily of diverse bacterial populations, possess the capacity to act as etiological factors in carcinogenesis and/or influence the individual's response to therapeutic interventions (107). There are limitations in case of microbiomics biomarkers for PCa specifically with PSA but still some of the biomarkers with increased expressions involved in the progression of PCa. Potential prognostic and diagnostic biomarkers for PCa are human endogenous retrovirus, herpes simplex virus derived HSV2-miR-H9-5p and HSV1-miR-H18 (108-111). No data exists on how microorganisms affect therapy response. Further investigation is required to explore the correlation between dysbiosis of the gastrointestinal tract and genitourinary microbiome, persistent inflammation and the development of PCa. Results could help develop innovative approaches and risk stratification methods (107). Some of the major microbiomics biomarkers associated with PCa are listed in table 4.

Table 4. Microbiome biomarkers associated with PCa.

Biomarker	Characteristics	Family	Stimulus	Molecular Targets	Role in carcinogenesis	References
E. coli	Gram-negative and rod-shaped	Enterobacteriaceae	Cytotoxic necrotizing factor 1 and Lipopolysaccharide	Toll-Like Receptor (TLR), CDC42 and Nuclear Factor kappa B (NF-Kb)	Avoidance of apoptosis, promoting inflammation and metastasis	(112)
Staphylococcus	Gram-positive and sphere-shaped	Staphylococcaceae	Staphylococcal enterotoxin	lncRNAs	Activation of immune system	(112)
Human papillomavirus	DNA virus	Papillomaviridae	E2, E6, and E7 (Enveloped proteins)	Tumor Necrosis Factor Alpha (TNF-α), Vascular Endothelial Growth Factor (VEGF), Interleukin 6 (IL-6), Reactive oxygen species (ROS), and NF-κB	Proliferation and survival of cancer cells	(112)
Adenovirus	Double-stranded DNA and enveloped	Adenoviridae	Fas ligand (FasL)	FasL-mediated apoptosis	Progression of cancer cells	(113)
Chlamydia trachomatis	Gram-negative	Chlamydiaceae	-	NF-κB, IL-6, TLR2-4 and FGF-2	Metastasis Vascularization	(114)

Future directions

Personalized medicine can facilitate the development of treatment strategies using omics. The early detection of PCa can prove to be a viable strategy, and additional investigations may yield more effective therapeutic interventions. Various omics technologies can aid in understanding the heterogeneity of tumor microenvironment of specific cancer types, thus helping in the development of a treatment. The current state of the diagnostic test does not permit its application in a clinical setting; further investigation is required to authenticate biomarkers, ascertain their therapeutic viability, and incorporate appropriate protocols. Miniaturized assays and multiplexing technology have the potential to facilitate the development of biomarker tests.

Conclusion

In this age of big data, researchers are using omics technologies like metabolomics, transcriptomics, and genomics to search for diagnostic markers in a wide range of diseases. Diagnostic research and disease surveillance in humans and economically relevant animals are two areas in which omics data are rapidly becoming crucial. This new era in clinical care calls for cutting-edge approaches, and lipidomics has been considered as one of the most promising. Health and economic benefits of the omics test should be established through prospective trials, and the test should be made more accessible to patients. Different novel targets and biomarkers can be identified for clinical applications by studying the oncometabolite and its association with different signaling pathways. The use of omics data has led to an improvement in the precision and dependability of diagnostic and prognostic assessments. Targeted therapy, when efficiently executed, has the potential to minimize the toxic effects on normal cells in comparison to chemotherapy.

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Conflicts of interest statement

Authors declare no conflict of interest.

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