Chapter 4

Biosensor Systems For Prostate Cancer Diagnosis: Principles, Advances and Clinical Perspectives

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Abstract

Prostate cancer remains one of the most prevalent malignancies among men worldwide, necessitating the development of rapid, sensitive, and reliable diagnostic methods. This chapter provides a comprehensive overview of biosensor systems developed for prostate cancer diagnosis, emphasizing their working principles, biomarker integration, and technological evolution. Key prostate cancer biomarkers—including prostate-specific antigen (PSA), PCA3, TMPRSS2-ERG gene fusion, microRNAs, sarcosine, and creatine kinase—are discussed in detail, highlighting their clinical relevance and application in biosensing platforms. The chapter also explores recent advancements in biosensor technologies, ranging from electrochemical and optical sensors to cutting-edge CRISPR/Cas-based, artificial intelligence (AI)-integrated, and smartphone-enabled biosensors. Particular attention is given to the design innovations that enhance sensitivity, specificity, and usability. Biosensors are anticipated to substantially improve the accuracy and availability of prostate cancer diagnoses, facilitating early intervention and superior patient outcomes.

1. Introduction

Prostate cancer (PCa) remains one of the most prevalent malignancies affecting men worldwide and represents a significant cause of cancer-related morbidity and mortality (1). Early diagnosis is critical for improving survival rates and treatment outcomes, yet current clinical diagnostic methods face several limitations. Prostate-specific antigen (PSA) testing, the most widely

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used biomarker for PCa, suffers from poor specificity and is prone to false-positive results due to benign conditions such as prostatitis and benign prostatic hyperplasia (BPH) (2,3). Moreover, PSA-based screening often leads to overdiagnosis and overtreatment, highlighting the urgent need for more specific, sensitive, and non-invasive diagnostic tools. In recent years, biosensors have emerged as promising diagnostic platforms capable of detecting prostate cancer biomarkers with high sensitivity, specificity, and rapid turnaround times (4). These devices integrate biorecognition elements with physicochemical transducers to convert biological interactions into measurable signals. Electrochemical, optical, and piezoelectric biosensors have been extensively explored for PCa diagnosis, targeting a range of biomarkers such as PSA, PCA3, miRNAs, and various protein markers (2,3,5). Advanced biosensors, including those based on nanomaterials, CRISPR/Cas technologies, and fiber-optic systems, have demonstrated remarkable performance enhancements, enabling the detection of biomarkers at extremely low concentrations (5,6). Among the innovative developments, electrochemical biosensors employing aptamers, gold nanoparticles, and screen-printed electrodes have shown excellent sensitivity in detecting PCA3 and PSA in biological fluids like urine and serum. Optical biosensors, including fiber-laser-based systems and quartz crystal microbalance (QCM) platforms, have been optimized for real-time, label-free detection of PCa markers, offering compact designs and potential for point-of-care applications (2,6,7). Furthermore, CRISPR/Cas12a-based biosensors have introduced a new dimension in prostate cancer diagnostics by enabling highly sensitive and specific detection of miRNAs associated with tumor progression (5). Recent studies emphasize the importance of multiplexed biosensing approaches and the integration of machine learning algorithms to improve diagnostic accuracy, especially in distinguishing between aggressive and indolent PCa (1,4,8). These advancements underscore the transformative potential of biosensors in clinical settings, paving the way for personalized medicine and more precise disease monitoring. As research progresses, the development of biosensor technologies targeting prostate cancer continues to evolve, driven by interdisciplinary innovations in nanotechnology, molecular biology, and data science (9). This chapter aims to provide a comprehensive overview of biosensor systems for prostate cancer diagnosis, focusing on fundamental principles, recent technological advancements, and their clinical perspectives.

2. Principles of Biosensors and Key Biomarkers

2.1. Biosensors: Basic Concepts and Functional Principles

Biosensors are analytical devices that integrate biological recognition elements with transducer systems to selectively detect target analytes by converting biochemical interactions into measurable electrical or optical signals (10,11). In electrochemical biosensors, enzymes play a crucial role by catalyzing highly specific reactions with the analyte, producing electroactive species such as hydrogen peroxide or enabling oxygen consumption, which can be detected by electrodes. These biosensors generally consist of integrated enzyme reactors, membranes, and electrode systems, where the catalytic reaction initiates a measurable electrical signal. However, challenges such as interference from other redox-active species and changes in physical parameters can impact selectivity. Redox mediators are frequently implemented to optimise biosensor performance and facilitate electron transfer, thereby facilitating enhanced sensitivity and a broadened detection range, thereby mitigating these challenges (10). Beyond electrochemical systems, other transduction mechanisms such as optical, piezoelectric, and thermal techniques are increasingly utilized in biosensors for biomedical analysis. Optical biosensors, for instance, convert biochemical interactions into measurable optical signals through changes in absorbance, fluorescence, or refractive index, allowing for rapid and label-free detection (11). These alternative platforms, alongside electrochemical systems, expand the versatility of biosensors across a wide range of clinical applications.

2.2. Prostate Cancer Biomarkers: Current Trends and Novel Targets

The most frequently employed clinical biomarker in prostate cancer (PCa) diagnostics is prostate-specific antigen (PSA). PSA testing enables early cancer detection but is limited by its low specificity, as PSA levels may also be elevated in benign prostatic hyperplasia (BPH) or prostatitis, leading to unnecessary biopsies and overtreatment (1,3,12).

Several alternative biomarkers have been investigated to enhance diagnostic accuracy. One of the most promising is prostate cancer antigen 3 (PCA3), a non-coding RNA highly specific to prostate cancer, detectable in urine samples. PCA3 testing, particularly when combined with PSA or TMPRSS2-ERG gene fusion analysis, significantly enhances diagnostic specificity (2,13). TMPRSS2-ERG, a common gene fusion event in prostate cancer, has emerged as another powerful biomarker that complements PCA3 and PSA to improve early detection rates (3,12).

MicroRNAs (miRNAs) such as miR-21, miR-141, and miR-375 have also been identified as potential non-invasive biomarkers due to their stability in body fluids and their role in cancer-related pathways (5,14). These miRNAs show strong potential for distinguishing prostate cancer from benign conditions and may also aid in prognosis and therapeutic monitoring (15). While its clinical value was initially debated, recent studies highlight sarcosine's potential for distinguishing aggressive prostate cancer cases, particularly in combination with genomic or transcriptomic biomarkers (13,16).

Creatine kinase has also been proposed as an emerging biomarker, offering insights into metabolic alterations associated with prostate cancer progression (9). Collectively, these biomarkers—when used in combination—offer promise for the development of multiplexed diagnostic panels, enabling more precise, non-invasive, and personalized prostate cancer detection strategies (4,13).

2.3. Biomarker Recognition and Interaction Mechanisms in Biosensors

Biosensors function through the selective interaction between a biological recognition element and a specific biomarker, triggering a measurable physicochemical signal. In prostate cancer diagnostics, biomarkers such as PSA, PCA3, TMPRSS2-ERG, miRNAs, and sarcosine serve as molecular targets that bind specifically to bioreceptors immobilized on the biosensor surface (17,18). These bioreceptors may include antibodies, aptamers, molecularly imprinted polymers (MIPs), or nucleic acid probes, depending on the biomarker's molecular characteristics and the detection strategy employed (19,20). The interaction between the biomarker and the bioreceptor results in a biochemical event, such as antigen-antibody binding, nucleic acid hybridization, or specific enzymatic reactions. This event induces detectable changes in electrical, optical, or mechanical properties at the biosensor interface (21,22). For example, in electrochemical biosensors, electron transfer or impedance changes occur upon biomarker binding, while in optical sensors, refractive index shifts or fluorescence changes are monitored (23,24). These signals are directly proportional to the biomarker concentration and are converted into quantifiable outputs through the transducer component of the biosensor. Critical to the performance of biosensors is the efficient immobilization of bioreceptors on the biosensor surface, maintaining their bioactivity and ensuring high specificity with minimal non-specific adsorption (25,26). Moreover, biosensors designed for prostate cancer diagnostics often incorporate surface modification

strategies, such as nanostructured coatings or antifouling layers, to enhance binding affinity and reduce background noise, thereby improving sensitivity and reliability in clinical settings.

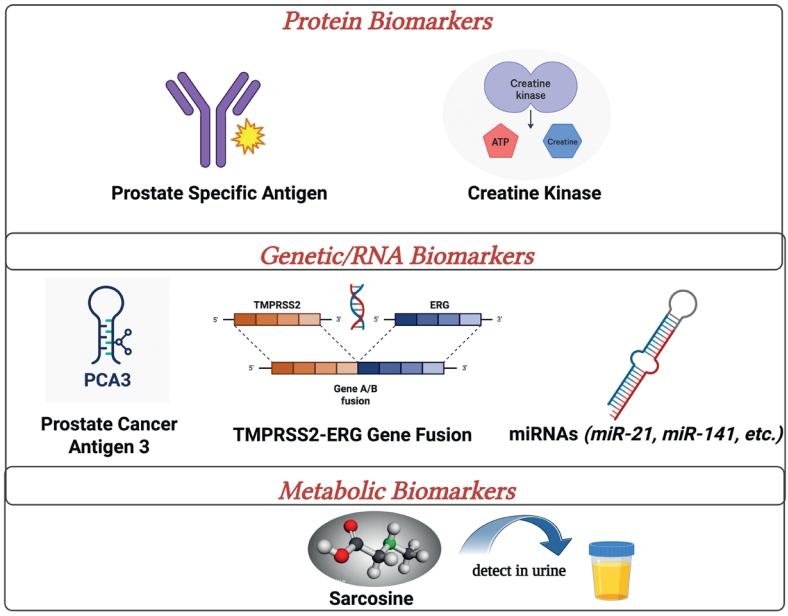

Figure 1. Classification of major prostate cancer biomarkers based on molecular category.

3. Recent Advances in Biosensor Technologies for Prostate Cancer

Biosensor technologies for prostate cancer diagnosis have evolved remarkably, transitioning from traditional electrochemical designs to advanced multi-modal and AI-integrated platforms. Early developments predominantly focused on electrochemical biosensors, particularly targeting PSA. These systems offered simple design, cost-effectiveness, and relatively high sensitivity, enabling point-of-care diagnostics for early-stage disease monitoring (3,7).

Subsequent innovations introduced aptamer-based biosensors with improved specificity and lower detection limits for PSA and emerging biomarkers such as PCA3. Notably, impedimetric aptasensors demonstrated exceptional label-free detection performance for PCA3, achieving sensitivities in the nanomolar range (2). These biosensors enhanced analytical accuracy while maintaining miniaturized, portable formats.

Simultaneously, microfluidic-integrated biosensors gained traction, combining immunosensing with lab-on-a-chip technologies to offer rapid, multiplexed detection of multiple prostate cancer biomarkers in a single assay. Such systems significantly reduced assay time and sample volume requirements, thus facilitating on-site diagnostics (6).

Nanomaterials and plasmonic nanostructures further revolutionized the field. Platforms employing silver nanocrystals and gold nanospikes enabled enhanced signal amplification for PSA detection, achieving unprecedented sensitivity levels suitable for early-stage cancer detection (4,7). Additionally, nanopore-based biosensors were developed for the precise identification of microRNAs such as miR-141-3p, offering label-free, high-resolution biomarker analysis at ultra-low concentrations (5).

Recent breakthroughs include artificial intelligence (AI)-integrated biosensors, capable of real-time prostate cancer screening by synergizing electrochemical transduction with machine learning algorithms. These systems enable automated result interpretation and enhanced diagnostic accuracy (27). Similarly, CRISPR/Cas-based biosensors have emerged as disruptive tools, enabling ultra-specific nucleic acid detection with rapid signal amplification, paving the way for next-generation prostate cancer diagnostics (28).

Moreover, nanozyme-assisted smartphone-integrated biosensors represent the forefront of personalized diagnostics, allowing highly sensitive, point-of-care detection of metabolic markers such as sarcosine with user-friendly interfaces (29). These devices demonstrate remarkable portability and accessibility, aligning with the global shift toward decentralized healthcare solutions.

Collectively, these innovations underscore the dynamic evolution of prostate cancer biosensors-from conventional electrochemical devices to cutting-edge AI-augmented and molecularly engineered platforms- each bringing new dimensions of sensitivity, selectivity, and clinical utility.

Table 1. Comparison of Recent Biosensor Technologies for Prostate Cancer Diagnosis

Biosensor Type	Target Biomarker(s)	Detection Method	Immobilization Method	Limit of Detection (LOD)	Reference
Electrochemical Biosensor	PSA	Amperometric	Carbon Nanotube-modified Electrode	0.1 ng/mL	(3)
Impedimetric Aptasensor	PCA3	Impedimetric	Aptamer + Gold Nanoparticles	1 fM	(2)
Microfluidic Biosensor	PSA, PCA3	Electrochemical + Microfluidics	Lab-on-a-chip, D-shaped Fiber	Multiplexed Detection	(6)
Optical Plasmonic Biosensor	PSA	Optical (Plasmon Resonance)	Gold Nanospikes	0.01 ng/mL	(7)
CRISPR/Cas12a Biosensor	miRNA (miR-141, miR-21)	Fluorescence, Nucleic Acid Ampl.	CRISPR/Cas12a with Dual Amplification	34 aM	(5)
AI-Integrated Electrochemical	PSA	Electrochemical + AI	Hybrid AI Algorithm with Electrochemical Sensor	0.01 ng/mL	(27)
Smartphone-based Nanozyme Biosensor	Sarcosine	Colorimetric	His@Co-NC Nanozyme + Smartphone Interface	5 μM	(29)

4. Conclusion

This chapter has comprehensively reviewed the principles, technological advancements, and clinical perspectives of biosensor systems developed for prostate cancer diagnosis. The discussion covered the fundamental mechanisms of biosensors, the most significant prostate cancer biomarkers, and their integration into various biosensing platforms. In particular, the growing shift from traditional electrochemical biosensors to innovative technologies such as aptamer-based biosensors, microfluidic devices, plasmonic systems, CRISPR/Cas platforms, AI-integrated biosensors, and smartphone-enabled nanozyme biosensors has been highlighted. The expanding importance of biosensors in prostate cancer diagnostics is evident from their ability to deliver rapid, highly sensitive, and non-invasive detection of both classical and emerging biomarkers. These technologies offer significant potential to overcome the limitations of conventional diagnostic methods, providing valuable tools for early diagnosis, risk stratification, treatment monitoring, and ultimately improving patient

outcomes. Looking forward, the future of prostate cancer biosensors lies in the continuous convergence of nanotechnology, artificial intelligence, and molecular diagnostics. The development of next-generation, cost-effective, and portable biosensors—capable of multiplexed detection and real-time analysis—holds promise for advancing personalized medicine and enhancing global access to reliable prostate cancer screening and monitoring tools.

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