ABSTRACT

Background

Early and accurate detection of prostate cancer remains a major clinical challenge due to the limitations of existing diagnostic modalities such as prostate-specific antigen (PSA) screening and invasive tissue biopsy, which often suffer from poor specificity and sampling bias. Gene-specific DNA methylation has emerged as a robust and early molecular signature of prostate cancer progression, offering significant promise for non-invasive and early diagnosis. However, conventional methylation detection techniques rely on chemical conversion, amplification, or labelling steps that compromise DNA integrity, limit multiplexing, and hinder translation to point-of-care platforms. This thesis aims to design and develop nucleic acid-based biosensing systems capable of direct, label-free detection of methylated DNA associated with prostate cancer, integrating molecular epigenetics with nanoelectronics to enhance diagnostic accuracy and clinical relevance while contributing to the innovation economy.

Material and Methods:

Methylation signatures of prostate cancer- associated genes were interrogated using a combination of biochemical discrimination strategies and nanomaterial-enabled transduction platforms. A Nucleic Acid-Based Radial Flow Assay (NABRFA) was initially developed to detect methylation-dependent DNA recognition using methylation-sensitive restriction digestion, enabling visual differentiation between methylated and unmethylated DNA without chemical conversion. Subsequently, WS,-based field-effect transistor (FET) biosensors were fabricated and biofunctionalized with gold nanoparticle-conjugated thiolated DNA probes for sensitive and selective electrical detection of methylated DNA targets. To achieve multiplexed detection, a WSe,-FET array was developed, integrating methyl-CpG binding proteins (MBPs) as biological recognition elements for simultaneous profiling of multiple gene-specific methylation signatures directly from genomic DNA samples.

Results and Discussion

Electrical measurements demonstrated distinct conductance modulation upon hybridization with methylated DNA, confirming that the WS -FET platform effectively transduces methylation-dependent molecular interactions into measurable signals. The WSe2-FETarray enabled simultaneous, label-free, and gene-specific detection, with MBPs discriminating methylated CpG regions in double-stranded DNA while preserving native methylation patterns. Studies using prostate cancer cell lines (LNCaP, PC-3) and a normal control (WI-38) revealed differential electrical responses consistent with known methylation hierarchies, demonstrating high specificity, reproducibility, and ultrasensitivity at femtogram levels. Validation through fluorescence-based MBP assays and MSRE-qPCR confirmed that the observed signals reflect effects. Collectively, these results establish a robust platform capable of early, minimally invasive

detection of prostate cancer epigenetic signatures, with direct relevance to patient care and translational diagnostic

Conclusion

This thesis establishes nucleic acid-based, nanomaterial-integrated biosensing platforms as a versatile, scalable, and clinically relevant approach for prostate cancer detection. By combining surface chemistry, molecular recognition, and nanoelectronic transduction, the developed systems provide label-free, multiplexed, and ultrahigh-sensitivity detection of promoter methylation. These platforms offer a clear pathway toward early diagnosis, improved patient care, and point-of-care liquid biopsy applications, representing a significant contribution to precision oncology and the innovation economy. The work lays the foundation for next-generation epigenetic diagnostics with strong potential for translational and commercial impact.