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Mini Review

MicroRNAs as biomarkers in prostate cancer: A mini review

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ABSTRACT

Among men one of the most common cancers identified globally is prostate cancer. Although the serum prostate specific antigen remains important for prognosis and diagnosis, the PSA assay is not highly accurate. In the search for improved minimally invasive methods as a biomarker, the expression patterns of circulating miRNAs have a potential importance and are emerging as a promising candidate as prognostic markers for prostate cancer.

1. Introduction

Prostate cancer [PCa] is a heterogeneous disease, ranging from small, indolent, low-grade tumours, to large, aggressive, life-threatening tumours. It is one of the common malignant tumours and is the third-leading cause of cancer-related deaths in the world. According to WHOs' projections for 2040, the number of deaths caused by PCa is expected to nearly double, while the number of newly diagnosed cases could reach 2,300,000 per year worldwide.[1] The occurrence of Prostate cancer differs substantially by race, ethnicity, and geography; these disparities may be attributed to differences in exposure to risk factors, access to screening and treatment and underlying biology of prostate carcinogenesis.[2] With the rising population, better average life expectancy, the epidemiological future predictions do not look promising.[3]

The patient care and outcome is fundamentally impacted by the diagnosis of prostate cancer and appropriate staging. Traditionally, a digital rectal examination (DRE) and a prostate-specific antigen (PSA) blood test have been used to identify prostate cancer (PCa). This is followed by a transrectal ultrasound (TRUS) guided biopsy.[4] After the introduction of the prostate-specific antigen (PSA) screening test, the detection of PCa has dramatically increased with a peak in the early 1990s.[5] Despite the significant improvement in early detection due to routine PSA testing, there are debates about its benefits because there is no consensus regarding whether it effectively reduces the risk of death from the disease. This is due to the fact that serum PSA levels are prostate but not cancer specific and fluctuate due to, for example, infections, inflammation, or benign prostatic hyperplasia (BPH), resulting in high false-positive rates. The poor correlation between PSA levels and disease state leads to unnecessary diagnoses and overtreatment of indolent PCa.[6]

With an ageing population, the number of prostate cancer cases will increase dramatically in the next few decades and represents a substantial public health burden. Although clinical parameters such as prostate specific antigen (PSA) value, imaging diagnostics and histopathological scores (e.g. Gleason score) allow certain risk stratification, they do not allow a definite statement about the individual patient's prognosis. This might lead to unnecessary treatment on the one hand, but also deny potentially favourable treatment on the other hand, and ultimately harm the patient.

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Consequently the current tendencies in the treatment course of patients with PCa increase the need for reliable biomarkers that help in decision-making in a challenging clinical setting.[7]

Henceforth beyond proteins and messenger RNAs (mRNAs), which have shown clinical utility in various clinical scenarios, there is a growing interest in the potential utility of microRNAs as PCa biomarkers. Around 2008, three independent studies demonstrated that tumour-associated miRNAs are released into the blood circulation and are present in human plasma and serum in a remarkably stable form.[8] More recently, cell free miRNAs have also been found in a variety of other biofluids.[9] Given that miRNA expression patterns are tissue and cancer-type specific, these findings led to the concept that different cancers may leave specific miRNA signatures in biofluids,[10] and that these signatures may carry information about the disease status, aggressiveness and response to therapy.

The miRNAs are evolutionarily conserved short (approximately 18–22 nucleotides) non-coding single-stranded RNA molecules that act as posttranscriptional gene regulators. The miRNAs are attractive molecular biomarker candidates because they can be reproducibly extracted from a wide range of biologic samples, do not require invasive biopsies and are generally stable and resistant to various storage conditions.[11] Importantly, miRNAs can be easily detected and accurately quantified by a variety of widely used standard techniques, such as qRT-PCR, microarray, and small RNA sequencing. The stability, lower structure complexity, and lack of modifications make circulating miRNAs to be ideal diagnostic biomarkers.

Following the initial discovery by Mitchell et al.[12] providing a proof of principle that miRNAs from prostate cancer cells are released in the bloodstream, where they are readily detectable by PCR-based methods, studies have explored miRNAs in biofluids and prostate tissue of prostate cancer patients. A summary of the known miRNAs associated with Prostate cancer is given in the Table 1.

2. Future Perspective

With a growing surge of research on miRNA as potential biomarkers in PCa, some questions are being answered, while many new ones are being asked. There is still no clear vision whether there is a distinct future for miRNA translation into clinical practice. On that account, additional research on all aspects of miRNA analysis right from preanalytics to clinical correlation in multiple, large cohorts may ensure an unambiguous conclusion.

Although there is still much work to be done before non-invasive miRNA biomarkers can begin to be used in the clinical setting, it is beyond doubt that miRNAs hold a significant promise as a potential non-invasive biomarker, creating a way for an individual patient-centred oncological approach in the near future.[14]

Table 1: MiRNAs as useful biomarkers in prostate cancer diagnosis and prognosis*[13]

Oncogenic miRNAs	Function
miR-21	Promotes tumour invasiveness and induces castration-resistance phenotype.
miR-221/miR-222	Enhance cell proliferation, invasion, cell survival, increaseclonogenicity and enhance tumorigenicity in vivo.
miR-141	Is important in androgen-dependent and in metastatic castration-resistant.
miR-375	Is important for an early diagnosis.
miR-18a	Promotes cancer progression.
miR-4534	Induces pro-cancerous characteristics in non-cancer cell lines.
miR-650	Suppresses the cellular stress response 1 (CSR1) expression.
miR-32	Inhibits apoptosis and enhances proliferation.
miR-106/miR-25	Facilitate tumour progression.
miR-125b	Enhances cell proliferation and inhibits apoptosis.

Table 2:

Tumour suppressor miRNAs	Function
miR-34a	Induces cell-cycle arrest, cell senescence and apoptosis and inhibits cell proliferation and cell invasion.
miR-145	Inhibits invasion, migration and arrests cell cycle.
miR-224	Inhibits invasion and migration of PCa cells.
miR-452	Regulates cell cycle, cellular adhesion and motility.
miR-200b	Inhibits PCa cell growth and invasion.
miR-382	Inhibits PCa cell proliferation, migration, invasion and metastasis.
miR-372	Inhibits proliferation, migration and invasion of DU145 cells.
miR-17-92a	Decreases cell cycle regulatory proteins and the expression of mesenchymal markers.
miR-27a	Suppresses MAP2K4 in the PCa cell.
has-miR-135-a-1	Inhibits cell growth, cell cycle progression, migration, invasion, and xenograft tumour formation.
miR-204-5p	Promotes apoptosis by targeting BCL2 in PCa cells.
miR-30a	Reduces expression of cell cycle protein, cyclin E2.
let-7 miRNAs	Regulate cell cycle, cell migration, cell proliferation and epithelial-to-mesenchymal transition progression.
miR-133/miR-146a	Suppress tumour progression via targeting EGFR.

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3. Conflict of Interest

None.

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