THE DISCOVERY OF *PCA3* AND ITS IMPLICATIONS ON THE DIAGNOSIS OF PROSTATE CANCER

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Abstract

Prostate cancer affects millions of men globally. In 2020, around 1.4 million new cases of prostate cancer were reported. Diagnosis of prostate cancer at an early stage is important for effective treatment and an increase in the overall survival rate of the patients. The Urology Department of the Radboud University Medical Center made the important discovery that the gene Prostate cancer-associated 3 or PCA3 is highly overexpressed in prostate cancer tissues. This launched the establishment of PCA3 as a biomarker for the diagnosis of prostate cancer and the development of a urine-based test for prostate cancer.

Introduction

Around 1.4 million new cases of prostate cancer were reported in the year 2020 with 375,304 men succumbing to the disease [1]. Prostate cancer is a major cause of death in men and is only second after lung cancer in cancer-associated mortality. The majority of men diagnosed with prostate cancer are above 60 years of age [2]. Prostate cancer arises due to mutations in the epithelial cells of the prostate gland. The prostate gland is a part of the male reproductive system and secretes important constituents that are a part of the seminal fluid. The disease can be confined to the prostate gland itself or become metastatic and disseminate into the lymph nodes, other organs and even to the bones. It is important to diagnose cancer when it is organ-confined as it can be treated by watchful waiting or by surgery combined with eternal beam radiation. Advanced disease requires androgen deprivation therapy, which involves blocking of the androgen receptor signalling pathway that is essential for the survival of prostate tumour cells. But tumours can become resistant to androgen deprivation therapy and they are then classified as castration-resistant prostate cancer. If these tumours disseminate into other parts of the body then the disease is termed metastatic castration-resistant prostate cancer, which ultimately becomes lethal [3].

The current diagnostic regimen for prostate cancer diagnosis includes Digital rectal examination, blood test for prostate-specific antigen (PSA), and Magnetic resonance imaging (MRI). Digital rectal examination involves the physical examination of the gland to check its texture, stiffness, and size. Additionally, prostate-specific antigen or the PSA test is used as serum levels are generally elevated in patients with prostate cancer [4]. However, these diagnostic techniques have a substantial risk for both false positives, detecting cancer when there is none, and false negatives, not detecting cancer whilst it is present. PSA levels might be elevated in case of inflammation, other pathological conditions or any physical stimulation of the prostate. Magnetic resonance imaging or MRI which involves the imaging of the prostate gland is a sensitive technique which helps detect the abnormalities present. Abnormal results of these tests prompt conducting a biopsy of the prostate gland so the presence of a tumour can be confirmed by histopathological analysis [2]. Especially the overdiagnosis of prostate cancer is cumbersome, as in such a case men will undergo unnecessary biopsies. It is therefore important to have a very definitive and characteristic biomarker for the diagnosis of prostate cancer. Having a reliable biomarker means that the risk of over-diagnosing and hence over-treating a patient is reduced. One such biomarker is the Prostate cancer-associated gene 3 or PCA3 [2].

The Discovery of PCA3 and its use for the diagnosis of prostate cancer

The fact that the Prostate cancer-associated 3 gene or PCA3 is selectively and overexpressed by prostate tissues was discovered by Bussemakers et al. at the Urology Department of Radboud University Medical Center [5]. Researchers analysed the mRNA expression levels of normal and tumour tissue samples of the human prostate. A nowadays old-fashioned technique called differential display analysis was used in this study. Using this technique, it was found that the PCA3 gene was overexpressed 10-100 times in the tumour tissue as compared to non-malignant tissue which was also confirmed by Northern blotting analysis. PCA3 expression is restricted to the prostate gland was proved by performing reverse-transcription polymerase chain reaction (RT-PCR) analysis, which revealed the absence of PCA3 in any non-prostatic tissue sample [5]. Later in next-generation sequencing analysis, it became clear that PCA3 is the most prostate cancer-specific transcript [6]. PCA3 is a long non-coding RNA. These are transcripts that do not code for any proteins and are more than 200 nucleotides long. They have been shown to be involved in a number of processes such as transcription of tumour suppressor genes and oncogenes, or regulation of genes involved in various signalling pathways [7]. There are also studies done that show that PCA3 silencing leads to a downregulation of vimentin which is a hallmark of cancer cells [8]. The exact role played by PCA3 is yet to be ascertained.

This discovery led to the establishment of the APTIMA PCA3 test (Gen-Probe Incorporated, San Diego, CA, USA)- a urine-based test for detecting the presence and expression level of PCA3 [9]. This urine-based test is minimally invasive, as it only requires a Digital Rectal Examination before collecting urine. The rectal examination is thought to release exfoliated tumour cells and extracellular vesicles ultimately into urine [8]. It is the only long non-coding RNA-based test that is approved for the diagnosis of prostate cancer [7]. This test is used for diagnosis in conjunction with other tests and is helpful in deciding whether a biopsy is necessary for a definitive diagnosis of the disease. The advantage of using a PCA3 test is that it is minimally invasive and cheaper than other tests [10]. It can also be used to decide whether a repeat biopsy for the patient suspected

for prostate cancer is necessary or not [9]. Repeat biopsies are taken when the first biopsies do not contain tumour tissue, the latter of which may be due to sampling error.

Future Perspectives

It is necessary to characterise the PCA3 long-non-coding RNA and unearth its function in the development and progression of prostate cancer. Understanding the roles played by PCA3 will help in the discovery of molecular mechanisms behind prostate cancer progression. It can also aid in the management of disease by monitoring the disease prognosis during treatment. Unravelling the roles played by this and other long-non-coding RNAs will also be important to develop therapies targeting the interaction partners of these RNAs.

Conclusion

Prostate cancer is one of the major contributors to deaths due to cancer. It is important to study the biomarkers that are associated with the disease so that it can be diagnosed at an early stage and adequately treated. The discovery of PCA3 proved to be an important milestone in this quest for a reliable biomarker. It is evident from the establishment of the urine-based PCA3 test that it was a very important discovery.

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