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DNA Hypomethylation in Prostate Cancer is Consistent

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Abstract

With approximately 1.4 million men diagnosed with prostate cancer each year around the world, PCa remains a terrifying threat to life and a source of devastating morbidity. Increased prostate-specific antigen screening and improved treatments have resulted in a significant decrease in age-specific PCa mortality in recent decades. Nonetheless, upcoming, enhanced PSA screening recommendations highlight an increasing disparity between the benefit and harm of current diagnosis/prognosis and application of radical treatment standards. To alleviate this tense situation, new powerful diagnostic and prognostic tools are unquestionably required. They should enable a more reliable early assessment of the impending threat, allowing for timely adjusted and personalised therapy and monitoring. We present here a basic study on an epigenetic screening method using Methylated DNA Immunoprecipitation.These can be used for early detection and may contribute to a new PCa epigenetic tumour classification system. Our findings show that we can isolate short, differentially methylated CpG-rich DNA fragments and combinations of them that are found in all tumours. Tumor cell-specific differential methylated CpG dinucleotide signatures are what we call them.

Keywords: Epigenetics • Hypomethylation • Diagnosis • Prostate cancer

Introduction

Prostate cancer is a devastating disease that threatens the health of every man, particularly in the last third of his life. In the United States, for example, the lifetime risk of being diagnosed with PCa is about 13%, and the lifetime risk of dying from PCa is about 2.5%. In 2020, the total number of new cases and deaths is expected to be 1,414,259 and 375,304, respectively. For many decades, clinical practise has largely remained unchanged in terms of PCa diagnosis standards and radical treatment methods. Nonetheless, they are not optimised or satisfactorily balanced in terms of benefit and harm, as acknowledged not only by experts in the field, but also by patients with the necessary knowledge.

As a result, it is critical to supplement current PSA testing technology with more sensitive and robust PCa biomarkers in order to reduce overtreatment, as well as to consider active surveillance and preserving therapies, such as high-intensity focal ultrasound, more frequently. Current DNA methylation biomarkers may be able to alleviate this situation. DNA methylation occurs at CpG dinucleotides scattered throughout the genome, many of which are organised in CpG dense clusters known as CpG islands and are associated with the 5′ regulatory regions of approximately 60% of the genes, as well as inter and intragenic CpG-rich regions with known or unknown regulatory function. Gene promoter methylation is linked to chromatin condensation and gene silencing, whereas gene promoter hypomethylation is linked to transcriptional initiation accessibility [1].

Description

It has also been demonstrated that differential methylation at individual CpG dinucleotides influences gene expression. These differentially methylated CpG signatures reflect the cellular composition of cellular mixtures and tissues, and have been linked to cancer prognosis. As a result, they have been suggested to be promising for cancer sample stratification. Several studies have already investigated CpG islands DNA methylation in PCa because aberrant DNA methylation associated with tumour suppressor and oncogenes is involved in the initiation and progression of carcinogenesis. As a result, novel differentially methylated genes that correlate with PCa and high-grade prostatic intraepithelial neoplasias, have potential functional consequences in PCa, or have the potential to distinguish PCa from adjacent benign tissue have been identified. These findings demonstrate the significance of abnormal DNA methylation in PCa.

To use cancer cell-associated differential methylation for diagnostic and prognostic purposes, however, a distinct differential methylated region (DMR) must consistently predominate in an early tumour stage and in a distinct class of tumours with a specific clinical behaviour. This is the foundation of a powerful biomarker that can achieve high sensitivities and specificities in clinical applications, first for early diagnosis and then for a reliable prognosis [2].

DNA hypomethylation is a common feature of carcinogenesis that affects a variety of cancers, including PCa. It is frequently observed during the early stages of tumorigenesis and becomes more pronounced as the tumour progresses or the degree of malignancy increases. Hypomethylation events have been linked to the reactivation of oncogenes, or genes involved in tumour invasion or metastasis. Furthermore, hypomethylation includes genome-wide distributed retrotransposons, such as LINE-1, which are thought to play a role in cancer. 1 hypomethylation rises with tumour grade and stage, and is especially noticeable in lymph node-positive prostate tumours. It has been proposed that in the future, DNA hypomethylation markers will be tested for methylation status in order to characterise cancers and design the best treatment for a specific tumour and individual [3,4].

To use differential methylation for diagnostic purposes, however, a high resolution DNA methylation screening analysis is required. Meanwhile, it is well established that, in addition to the classical epigenetic dogma depicting DNA methylation at CpG islands as an inhibitor of gene expression, genome-wide distributed DNA methylation at CpG dinucleotide resolution plays functional roles in chromatin plasticity, gene regulation, and splicing. Furthermore, the meticulous computational biology analysis of our CpG islands data encouraged us to pay special attention to the inspection of the CpG-rich 60 bp probes used in our DNA methylation array analyses in order to improve resolution. Finally, we discovered hypomethylated CpG-rich probes that were present in all 20 tumour samples from clinical centre No. 3.

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According to The Cancer Genome Atlas PCa expression data bank, they are associated with overexpression. Furthermore, the literature demonstrated their critical role in PCa and cancer. It is possible to combine several of these promising markers to further investigate their potential for clearly distinguishing PCa in, for example, mixed tissues from suspect biopsies. Following this strategy, we would select DMRs associated with NOTCH3, whose overexpression has been associated with lymph node metastasis, higher pT stages, higher pathological tumour stages, and groups of higher grades, all of which reflect features of aggressive PCa tumours [5].

Conclusion

Based on methylated CpG-rich probes of 60 nucleotides, our hierarchical clustering analyses show that it is possible to classify PCa samples into distinct groups. The correlation with distinct clinical features of these subgroups could lead to a useful new epigenetic tumour classification system for PCa, particularly if we can limit this analysis to functionally relevant hypomethylations while excluding all pleiotropic and inconsistently occurring hypomethylations. Finally, Panther analyses applied to our data reveal, among other things, angiogenesis, NOTCH, Toll receptor, WNT, and p53 signalling pathways as major pathways involved in PCa, implying that distinct, previously unknown cryptic hypomethylation events underpin those well-established PCa associated pathway alterations.

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Conflict of Interest

There are no conflicts of interest by author.

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