Cancer Letters 342 (2014) 248–256

Contents lists available at SciVerse ScienceDirect

Cancer Letters

journal homepage: www.elsevier.com/locate/canlet

Mini-review

Epigenetic biomarkers in prostate cancer: Current and future uses

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ARTICLE INFO

Keywords:
Prostate cancer
Epigenetics
Biomarkers
DNA methylation
Histone modifications
MicroRNAs

ABSTRACT

Epigenome alterations are characteristic of nearly all human malignancies and include changes in DNA methylation, histone modifications and microRNAs (miRNAs). However, what induces these epigenetic alterations in cancer is largely unknown and their mechanistic role in prostate tumorigenesis is just beginning to be evaluated. Identification of the epigenetic modifications involved in the development and progression of prostate cancer will not only identify novel therapeutic targets but also prognostic and diagnostic markers. This review will focus on the use of epigenetic modifications as biomarkers for prostate cancer.

1. Introduction

Prostate cancer is one of the most commonly diagnosed cancers in men of developed Western countries. Globally, it is the 2nd most commonly diagnosed and 6th leading cause of cancer death in men [1]. Several risk factors such as family history, race, obesity, diet and other environmental factors have been associated with prostate cancer. The best established risk factor for prostate cancer is age, whereby there is an estimated incidence of 80% in men by 80 years of age [2]. Hence, prostate cancer is globally a major health and economic burden in our current aging population.

When diagnosed at an early organ-confined stage of the disease, prostate cancer is potentially curable by radical prostatectomy, which involves the removal of the prostate gland, and/or radiotherapy. However, it has been estimated that approximately 30% of patients relapse after the initial treatment. Since the discovery in the 1940s that prostate cancer is dependent on the male sex hormones androgens [3], the main therapy for patients diagnosed with metastatic disease or progressive disease, targets androgen production and its mediator, the androgen receptor (AR). These therapies, called hormonal or androgen ablation therapy, refers to the administration of anti-androgens that block the functional action of AR [4]. After an initial period of tumor regression, prostate cancers become unresponsive to these therapies and eventually progress to the "castrate-resistant" state. Currently, there is no curative treatment available for castrate-resistant prostate cancer, and chemotherapy has limited benefits in improving survival.

2. Current prostate cancer biomarkers: PSA

Because of the limitations of current treatments, one of the major clinical problems for prostate cancer is to decide what treatment options may be the best for individual patients at the time of diagnosis. Prostate cancer is extremely heterogeneous and can present either as indolent or aggressive disease. Since most prostate cancer occurs in elderly men, patients with indolent disease will die with prostate cancer rather than die from the disease. Therefore, it is important to consider whether it is actually beneficial for these men to go through "unnecessary" treatments that may cause complications and affect their quality of life without contributing to any survival benefits. Unfortunately, there is no biomarker available for prostate cancer to predict disease progression at the time of diagnosis. The only biomarker currently used for the detection and monitoring of treatment efficacy for prostate cancer is the measurement of serum prostate specific antigen (PSA) levels and there is constant debate as to whether PSA actually aids in the management of prostate cancer for the following reasons [5,6]:

(1) There are no distinct cut-off serum PSA levels that absolutely define if a patient does have prostate cancer. Although a high serum PSA level is indicative of the presence of prostate cancer cells, studies have shown that a proportion of men without prostate cancer have high levels of

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doi:10.1016/j.canlet.2012.02.011

serum PSA [7] and about 22% of men with prostate cancer have been found to have low serum PSA levels [8]. This means that a proportion of men will undergo the unnecessary invasive procedure of a needle biopsy, while a proportion of men will have their prostate cancer undetected.

(2) PSA is not a prostate cancer specific marker. An increase in serum PSA level may indicate the presence of other prostatic diseases such as benign prostatic hyperplasia (BPH), which is also common in elderly men (75–90% incidence in men by the age of 80 years) [9,10] and prostatitis.

(3) Serum PSA levels are not able to distinguish patients with indolent disease from those with aggressive prostate cancer at the time of diagnosis. In addition, the current early detection of prostate cancer results in most patients presenting with a low stage/grade prostate cancer, making the clinical decision about whether and how to treat the patient difficult. Particularly in the case for elderly men with an expected life expectancy of less than 10–15 years, clinicians have to decide whether these patients will have a survival benefit from treatment or if watchful waiting is the best option.

(4) Using serum PSA levels to determine treatment efficacy requires monitoring over a period of time before a clinician can decide if the treatment is suitable for a patient. For instance in the case of chemotherapy, the clinician is not able to predict if a patient is responsive to the treatment until after a prolonged treatment period that may be accompanied by unpleasant side-effects.

Recently, two large trials investigated the effect of PSA screening test and survival benefits of prostate cancer patients in the US (n = 76,693 men) and Europe (n = 182,000 men) with contradicting results [5,6]. The US study reported no significant difference in prostate cancer mortality between patients who underwent annual PSA screening test compared to the control group, while the European study reported a 20% decrease in prostate cancer mortality due to PSA screening. A meta-analysis on a total of six randomized controlled trials, including the above US and European trials, did not support the usefulness of PSA screening on prostate cancer mortality [11].

Although there are continued efforts to find better biomarkers or improve PSA measurements (i.e. free PSA, total PSA, PSA velocity) for prostate cancer, no biomarkers investigated so far seem to provide any additional diagnostic/prognostic value than serum PSA [12–14]. In this continuous search for new biomarkers for prostate cancer, accumulating evidence for the role of epigenetic modifications in prostate tumorigenesis suggests that they may be candidate biomarkers for prostate cancer. In this review, we shall discuss the previous studies investigating candidate epigenetic biomarkers for prostate cancer, the challenges we face and the latest advancement in this area of research (see Table 1).

3. Epigenetic modifications

Epigenetic modifications are heritable and reversible biochemical changes of the chromatin structure [15–20]. Unlike mutations that involve an alteration in the DNA sequence, epigenetic modifications regulate gene expression via chromatin remodeling [21–23]. Three of the most well studied epigenetic modifications are DNA methylation, histone modifications and microRNAs (miRNAs).

DNA methylation is the addition of a methyl group from methyl donor S-adenosylmethionine to the 5′ carbon of the cytosine predominantly at the cytosine and guanine (CpG) dinucleotides [24,25]. This chemical reaction is catalyzed by a group of enzymes known as DNA methyltransferases (DNMTs) [26,27]. CpG islands, which are clusters of CpGs, are frequently found within gene promoter regions [28]. In contrast to CpG dinucleotides dispersed within the genome or in DNA repetitive elements that are normally methylated, gene-promoter associated CpG islands are usually unmethylated. DNA methylation of promoter-associated CpG islands is associated with gene repression, either through a direct or indirect influence on the chromatin structure that ultimately results in chromatin condensation [25,29–32].

In comparison to DNA methylation, histone modifications are more dynamic and complicated class of epigenetic modifications. In a "closed" and repressed chromatin conformation, the basic amino acid residues (i.e. lysine, arginine and serine) on the N-terminal tails of histones have a high binding affinity to the negatively charged DNA [33]. Histone modifications such as acetylation, phosphorylation and methylation refer to the addition of these specific biochemical groups to the basic amino acid residues on the N-terminal tails of histones [17,19], which alters the affinity of the histone tails to the DNA and results in a conformational change in the chromatin structure that alters gene transcription [17,19]. For example, histone acetylation is associated with active gene transcription while removal of the acetyl groups by histone deacetylases (HDACs) results in subsequent gene repression [21,34,35]. Conversely, histone methylation includes the addition of one or more methyl groups to H3, H4 lysine and arginine residues (mono-, di- or tri-methylation) and has been associated with either activation or repression of gene transcription depending on the target residue and nature of the modification [23,28,36,37]. It is the combination of histone modifications (histone code) and co-operation with DNA methylation that determines the chromatin state and outcome of a gene readout [38].

MicroRNAs (miRNAs) are small non-coding RNAs of approximately 22–25 nucleotides, exist naturally in the genome and are involved in numerous cellular functions like development and differentiation [39]. These miRNAs can bind to complete or partial complementary mRNA targets (a single miRNA is able to target multiple genes), usually at the 3′-untranslated region, to induce gene silencing by mRNA degradation or translational repression [40,41]. miRNAs can induce gene silencing via epigenetic mechanisms, for instance, by targeting a specific gene region for DNA methylation and histone modifications [42,43]. Studies have also identified specific miRNAs that can regulate expression of epigenetic enzymes like the DNMTs, leading to a more global influence on epigenetic regulation [44,45]. Furthermore, the expression of miRNAs themselves may also be regulated by epigenetic mechanisms (i.e. silenced upon DNA methylation), demonstrating the close interactions between miRNAs and other epigenetic mechanisms [43,46,47].

4. Epigenetic modifications as biomarkers for prostate cancer

Epigenetic alterations are frequent in prostate cancer and are thought to contribute both to the disease initiation and progression [22,24,48,49]. Although the exact mechanisms of how these epigenetic alterations arise in prostate cancer are not understood, the fact that they occur at a much higher frequency than mutations and are common in premalignant stages of the disease make them attractive biomarkers for diagnosis, prognosis and treatment response (Fig. 1) [50].

4.1. DNA methylation-based biomarkers: GSTP1

The most frequently studied epigenetic modification in prostate cancer is DNA methylation. Hence, many studies investigating