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Identification of DNA methylation biomarkers predicting prostate cancer aggressiveness

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Abstract

Prostate cancer (PCa) is the most commonly diagnosed cancer and second leading cause for men in the United States. The majority of prostate cancer (PCa) detected in the era of routine prostate-specific antigen (PSA) screening are indolent and pose little or no threat to the health or longevity of the patients. However, about 90% of men with localized PCa receive aggressive treatment that often causes significant morbidity. This clinical dilemma is largely attributed to the fact that clinical variables, such as Gleason Score (GS), PSA level, and tumor stage, cannot accurately predict aggressive from indolent diseases at diagnosis. It is imperative to find biomarkers that can augment clinical variables and improve risk stratification of PCa patients. The clinical utility of tissuebased biomarkers is limited by the invasive procedure, false negative biopsy, and tumor heterogeneity. Blood is easily accessible and measures systemic effect. In this seminar, I will focus on blood-based biomarkers: Global DNA methylation and specific locus methylation. I will discuss methylation biomarkers that we have found, how to apply estimate the specificity and sensitivity of newly found biomarkers and establish multivariate nomograms that include epidemiological factors, clinical variables, and biomarkers. Thus, there is major interest in identifying new molecular biomarkers to complement existing standard clinicopathological markers. DNA methylation is a frequent alteration in the cancer genome and offers potential as a reliable and robust biomarker. In this review, we provide a comprehensive overview of the current state of DNA methylation biomarker studies in prostate cancer prognosis. We highlight advances in this field that have enabled the discovery of novel prognostic genes and discuss the potential of methylation biomarkers for noninvasive liquid-biopsy testing.

There is a major clinical need for accurate biomarkers for prostate cancer prognosis, to better inform treatment strategies and disease monitoring. Current clinically recognised prognostic factors, including prostate-specific antigen (PSA) levels, lack sensitivity and specificity in distinguishing aggressive from indolent disease, particularly in patients with localised intermediate grade prostate cancer. There has therefore been a major focus on identifying molecular biomarkers that can add prognostic value to existing markers, including investigation of DNA methylation, which has a known role in tumorigenesis. In this review, we will provide a comprehensive overview of the current state of DNA methylation biomarker studies in prostate cancer prognosis, and highlight the advances that have been made in this field. We cover the numerous studies into well-established candidate genes, and explore the technological transition that has enabled hypothesis-free genome-wide studies and the subsequent discovery of novel prognostic genes.

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