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Field effect-a New Idea for Early Diagnosis of Prostate Cancer*

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ABSTRACT: To diagnose prostate cancer, many repeat biopsies are needed in patients with prior negative biopsies to prevent missed diagnosis. Though prostate cancer might be detected by repeat biopsies in some patients, many other patients will never be diagnosed with this disease confirmed by long term follow-up and lots of unnecessary biopsies. Recent findings supported histological normal appearing tissue which adjacent to tumor focus, would develop similar molecular changes like cancer. Therefore, we believe that there is a field effect in the procedure of prostate cancerization. By the instruction of this theory, selecting proper marker and detecting its alteration in prostate, clinicians will be able to predict the development of prostate cancer before affirmation of this disease by routine pathological result. It means these patients should be followed closely and carried out more extensive repeat biopsies soon to confirm PCA earlier, while other patients scarcely of this marker in their prostate might possibly be followed less frequently and aggressively. If the confidence of markers reflecting the theory of field effect can be confirmed by further large cohort diagnostic trials, the current situation of prostate cancer diagnosis will be greatly changed.

Key words: Prostatic neoplasms; Diagnosis; Field effect; Biopsy

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Introduction

Nowadays, prostate cancer (PCA) is the most prevalent form of cancer in men and the second leading cause of cancer death in the United States, and the third most common cancer in men of worldwide[1]. As clinical signs of PCA only appear at a later stage, early detection is vital.

The main tools for screening PCA include digital rectal examination, serum concentration of prostatic-specific antigen levels and transrectal ultrasonography [2]. But the diagnosis of PCA still depends on the presence of adenocarcinoma in operative specimens, prostate biopsy cores or aspiration needle cytology. Since Hodge first introduced transrectal ultrasound guided prostate biopsy, it has become the standard method for diagnosis of PCA [3].

Although most cancer is found at the initial biopsy, more than 70% patients are left with doubt regarding the presence of PCA[4]. As expected from any such patient cohort, a significant proportion of PCA cases are routinely missed due to the obvious difficulty of sampling a small tumor within the whole prostate. Many small tumors can escape being sampled. Besides the biopsy technique has been improved and the number of cores for single biopsy greatly increased, the false-negative rate by single biopsy is still relatively high, remaining at about 30% [5,6], which is far from satisfactory. Even patients, who have agreed to accept more extensive biopsies, may still have significant PCA detection rates in repeat biopsies [7]. Negative biopsy raises an important clinical dilemma, namely what to do with the patient at this time, which finally results in the need for a great number of repeat biopsies on patients with prior negative biopsies to prevent missing the PCA which already exist probably. Though PCA might be detected by repeat biopsies in some patients, the opportunity of surgery may be lost by the long period of diagnosis. While other patients will never be diagnosed with this disease throughout their lives, but they have to suffer from severe stress, unnecessary pain, and expensive medical cost [8].

As yet, no parameters have been agreed that would prevent a patient in this situation undergoing an unnecessary repeat biopsy. To our opinion, a new method that could identify individuals with negative biopsies who do have PCA undetected by biopsy, and differentiate them from those who do not have the disease would be of great benefit.

1 Field effect theory of carcinogenesis

Field effect, which is also known as field cancerization, is well documented process of malignant transformation.

Early to 1953, Slaughter et al. proposed the term field cancerization to explain the presence of multifocal head and neck cancers developing out of a field of precancerous change that had developed as a consequence of carcinogen exposure [9].

This theory was expanded by Braakhuis et al. who proposed that the field was in fact a clonally expanded area of mutated cells [10]. Clonally expanded mutated patches have been noted previously in dysplastic and phenotypically normal mucosa of colitis patients [11,12]. Multistep field cancerization indicates two levels of cancer progression: molecular progression whereby histological normal

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looking cells undergo sequential cumulative acquisition of genomic damage, and phenotypic progression whereby a neoplastic cell accumulates genetic alterations and undergoes further phenotypic changes (e.g., from intraepithelial neoplasia to various stages of invasive cancer).

Significantly, evidences for such malignancy associated changes have been found in other organs such as bladder [13], cervix [14] and breast [15].

Some researchers have also observed similar phenomenon from PCA. Yu et al. have explored the feasibility of predicting PCA aggressiveness by gene expression analysis [16]. To their surprise, the heterogeneity in gene expression is not only limited to cancer region. There were 1022 genes differentially expressed in prostate tissue adjacent to cancer samples in comparison with donor prostate tissue which totally free of this disease. And most of these genes (more than 70%) were similarly altered expression in tumor samples. This serendipity suggested that the patterns of gene expression in tissue adjacent to cancer are much more similar to cancer focus than donor prostate, supporting the "field effect" hypothesis. The study of Chandran et al [17] provided further evidences for Yu et al [16]. On the other hand, Mehrotra et al. have investigated the magnitude and spatial dependence of the field effect by measuring methylation ratio of several relative biomarkers at different location in prostatectomy sample [18]. The results revealed that RARβ2 showed the most pronounced field effect which up to 3 mm from the malignant core in prostate. And they believed that the Examination of RARβ2 methylation status in conjunction with histology could decrease the false negative rate in prostate biopsy and may provide prognostic value.

2 Clinical implications

An important clinical utility of field cancerization is in complementary evaluation of pathologic biopsy specimen. Currently, biopsies for PCA diagnosis are reviewed by histology - the gold standard, and the absence of abnormal cells often precludes the diagnosis of cancer. However, histological normal biopsy specimen that possess molecular signatures of cancer fields suggest either the tumor was missed by the biopsy procedure, or that some cells in the tissue are progressing towards malignancy. Such high risk patients will require close surveillance for early detection of this disease.

In this paper, we propose the hypothesis that PCA could also show field effect - histological normal appearing tissues adjacent to cancer focus, would develop similar molecular changes like cancer.

It is reasonable to speculate that genetic alterations occur even before cells are morphologically transformed. Therefore, we believe that detecting and monitoring of altered expression of proper biomarkers being able to reflect field effect, could identify individuals with PCA significantly earlier than they are currently diagnosed. In addition, it could allow us to limit the numbers of repeat biopsies that would need to be used for clinical evaluation.

Based on this theory, several markers for PCA field effect which meeting above-mentioned demand have been developed, such as early prostate cancer antigen (EPCA) [19,20] and non-functional cytolytic $P2X_7$ receptors [21,22], which showed superior sensitivity and specificity in small diagnosis trials, and almost solved the paradox of misdiagnosis of PCA perfectively.

Dhir et al have reported that a significantly higher level of constitutive Stat3 activity could be detected in both prostate carcinomas and matched normal prostate tissues adjacent to tumors compared to normal prostates from donors without prostate cancer [23]. Based on this observation, we carried out a research of detecting P-STAT3 expression for early detection of PCA, and received relative satisfied results as followed: on one hand, P-STAT3 might be a proper marker for field effect of PCA which expressed in adjacent normal tissues as tumor focus but absent for tissues from prostates without tumor; on the other hand, P-STAT3 could be used as a candidate diagnostic tool for selecting PCA patients from population of negative biopsies with a relative high accurate (80.8% for sensivity, and 76.3% for specificity); last but not the least, this program could indicate the development of PCA earlier than current diagnostic routine for PCA [24].

Subsequent investigations with larger patient sets designed as prospective and retrospective studies will be needed to evaluate the usefulness and efficacy of these markers of PCA field effect in the clinical arena. Depending on the results of these studies, there will be a need to design new algorithms for evaluation and assessment of patients with suspected PCA [25]. Patients selected by field effect markers for suspect PCA, should be followed closely and carried out more extensive repeat biopsies soon to confirm PCA earlier, while other patients left by these markers might possibly be followed less frequently and aggressively.

3 Conclusions

To our knowledge, early detection of PCA is a key to complete cure and ideal prognosis. But current diagnostic program with prostate biopsy was far from satisfaction. The process of carcinogenesis often involves stepwise progression of molecular events. These processes are represented by the presence of field effect in the adjacent normal tissues. Based on this theory, detecting proper markers capable of reflecting field effect may act as an adjunctive to the current diagnostic method by selecting individuals who have cancer foci that are unfortunately missed by initial biopsy who should be carried out repeat biopsies soon for earlier diagnosis of PCA, while other patients left by these markers might be confirmed as free of PCA and followed infrequently and mildly.

Although the mechanism of the theory of field effect is still unclear, the current situation of PCA diagnosis will be greatly changed by validating the confidence of markers reflecting this theory by further large cohort diagnostic trials for PCA.

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区域效应－一个前列腺癌早期诊断的新思路*

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摘要:目前临床上有许多怀疑前列腺癌但穿刺阴性的病例,为了避免漏诊,多数患者必须接受重复穿刺。尽管部分患者经重复穿刺确诊为前列腺癌,而更多患者经过长期随访以及反复穿刺最终确诊为良性病变。近期研究证实,癌灶附近的组织学表现正常的组织中也可发生与癌灶相似的分子改变。因此,我们认为在前列腺癌的发生过程中存在区域效应。在这一理论指导下,选择适当的可反映前列腺癌区域效应的标记物,在穿刺阴性的标本中检出与癌灶相似的分子改变,就可以帮助临床医生在常规病理诊断之前,提前预测前列腺癌的发生。如果能够找到这样的标记物,并在大规模的诊断试验中证实其可行性,那么就可以极大地改善前列腺癌诊断的现状。

关键词:前列腺肿瘤;诊断;区域效应;活检
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