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EDITORIAL

Non-Invasive Biomarker in Prostate Carcinoma: A Novel Approach

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World-wide, prostate cancer (PCa) is one of the commonest cancers in men affecting 33 % of global burden. The prostate biopsy remains invasive method for detecting PCa and currently, serum prostate-specific antigen (PSA) is considered as one of the best available tumor marker for detecting PCa at early stage which also has prognostic value. However, there are certain limitations of PSA in which the most important one is that it is prostate-specific and not cancer specific. Further its serum level also rises in many conditions like benign enlargement and prostatitis. The sensitivity and specificity of PSA is also controversial as it varies from 0.78 to 1.00 and 0.06 to 0.66, respectively [1]. With better understanding of the molecular mechanisms of carcinogenesis and revolutionary advancement of novel sub-branches of molecular biology such as genomics, epigenetic, transcriptomics, proteomics, metabolomics, lipidomics etc., and newer imaging techniques have now open new vistas in the field of biomarkers discovery. Many newer molecules are being examined especially in cases of non-invasive procedures, thus clinical oncology is poised to enter a new era in which cancer detection, diagnosis, and treatment is guided increasingly by the molecular attributes of the individual patient, acquired from several different sources that influence tumour behavior and body fluids.

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Genomics/Epigenetic and SNPs

Over the past two decades epigenetic has broadened its field and played an important role in the study of cancer genetics. Epigenetic gene regulation refers to non-coded heritable changes in gene expression which includes DNA methylation, histone modifications and noncoding RNA-induced transcriptional changes. These are required for the transcriptional regulation and genomic stability. Two histone modifiers—HAT p300 and HDM EZH2—are promising PCa biomarkers which have shown to be over expressed in PCa and its expression levels precisely correlated with various disease stages [2]. This feature may make it a standard dual biomarker.

Hypermethylation and gene silencing have been documented for cell cycle regulation such as anaphase promoting complex (APC) and Ras association domain-containing protein 1 (RASSF1a), detoxification enzymes e.g., glutathione S-transferase Pi 1 (GSTP1). Moreover, a combined assay for GSTP1 and APC hypermethylation have great potential for detecting PCa in clinical samples up to 100 % sensitivity [3, 4].

The risk of PCa can also be estimated from single nucleotide polymorphisms (SNPs) of alleles in different region of chromosome (EHBP1, THADA, ITGA6, EEFSEC, PDLIM5, FU20032, SLC22A3, JAF1, LMTK2, NKX3, CMYC, MSMB, CTBP2, HNF1B, KLK2-3, TNRC6B, BIK, NUDT10-11) which influence the behavior of the disease and its progression by changing expressions of mRNA and protein. This has been examined and documented in more than 9,000 patients (9893–61, 388 patients) [5].

Transcriptomics

The noncoding RNA (ncRNA) is a relatively new field in PCa research. The term ncRNA encompasses the well-studied

functional RNAs like rRNA and tRNA, as well as microRNA (miRNA; previously known as small ncRNA) including long ncRNA (lncRNA) and small interfering RNA (siRNA). Three known lncRNAs which have shown their importance in detecting, screening and monitoring PCa [6] because of their high specificity and sensitivity are PCa non coding RNA-1 (PRNCR1), prostate-specific gene 1 (PSGEM1), and PCa antigen 3 (PCA3); also referred to as differential display 3 (DD3). Recently it has also been proposed that PCGEM1 gene, which encodes a lncRNA is highly prostate-specific. Further the screening of TMPRSS2-ERG fusion (TEF) techniques as assessed by Immunohistochemistry, FISH and RT PCR found to have significance in the diagnosis PCa. However the TE fusion in combination with PCA3 mRNA may prove more beneficial in diagnosis [7].

Circulating microRNAs (miRNA) have recently been supposed to be a biomarkers for non-invasive diagnosis in various tumors. Studies based on oligonucleotide array hybridization miRNA profiling have identified that ~51 miRNAs are differentially expressed between benign and malignant prostate tumors, of which 37 were down-regulated and 14 up regulated. These differentially regulated miRNAs lead to changes in the expression and activity of their targets in PCa [8]. The miRNA expression alters with the development and progression of PCa as some of the cancer-related genes are regulated by them and thus its dysregulation has significance in PCa. Using a mouse xenograft model, Mitchell et al. [9] has demonstrated that miRNAs originated from the human PCa xenografts enter the circulation and thus reported that miR-141 is up regulated in sera of metastatic PCa patients which can distinguish PCa patients from healthy controls with high sensitivity and more accuracy.

The Metabolomics is also promising in the diagnosis as few genes involved in metabolism and needed for increased energy demand in tumor cells are upregulated e.g. genes involved in fatty acid metabolism including the multi-enzyme protein, fatty acid synthase (FASN) [10]. Further, the DNA micro-array studies and meta-analysis have also reported the over expression of the hepsin (HPN) gene in primary PCa.

Proteomics

Proteomics also play an important role in the field of biomarker specially in non-invasively collected bio fluids as for prognosis [CGRP, VEGF, endoglin (CD105), chromogranin-A, neuron-specific enolase, interleukin-6 transforming growth factor-β, other methylated genes including RASSF1α, APC, RARB2 and CDH1, prostate-specific cell antigen, testosterone, estrogen, sex hormone binding globulin, caveolin-1, E-cadherin, β-catenin, MMP-9, tissue inhibitor of MMPs (TIMP 1, 2) progastrin-releasing peptide (ProGRP 31–98)] and PSP94, ZAG, prostasome (auto-antibodies), huntingtin-interacting protein 1 (auto-antibodies), TSP-1, leptin, ILGF-1, -2, human kallikrein 2, α-methylacyl-CoA racemase (auto-antibodies), early prostate cell antigen-1, -2, *GSTP1* hypermethylation, cytokine macrophage MIF, hK11, apolipoprotein A-II for diagnosis. Few as urokinase—type plasminogen activator system, prostate membrane-specific antigen, hepatocyte growth factor, MIC-1, EGFR family (c-erbB-1 (EGFR), c-erbB-2 (HER2/neu), c-erbB-3 (HER3) and c-erbB-4 (HER4) [11] have shown their equal potency in diagnosis as well as prognosis. More recently Dwivedi et al. [12] have proposed circulating serum interleukin-18 as a diagnostic biomarker and interleukin-10 for prognosis.

Metastatic castration resistant PCa (MCRPCa) and metastasis associated protein-1 (MTA-1) have been widely explored for their role in PCa mainly in vascularization of the progressing tumor [13]. The significance of WNT5A, EZH2, MAPK pathway members, AR, various androgen metabolism genes are also over expressed in metastatic PCa and *c-FOS jun B* down-regulated thus also have significance as biomarker. Other potential molecular markers for this cancer which are reportedly over expressed are human kallikrein-related peptidase 2 (hK2), early PCa antigen (EPCA), α-methylacyl-coA racemase (AMACR), insulin-like growth factors and binding proteins (IGFBP-2and IGFBP-3), TGF-β1, elevated circulating levels of the interleukin-6 (IL-6), and its receptors, urokinase plasminogen activator (uPA) and receptor (uPAR), enhancer of zeste homolog 2(EZH2), and prostate-specific membrane antigen (PSMA) [14].

These biomolecules have shown their importance but still away from hitting the target more accurately and precisely. Thus we should look forward for more specific and sensitive biomarkers which can differentiate PCa into various stages more precisely and accurately.

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