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REVIEW

Research status and progress of the RNA or protein biomarkers for prostate cancer

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Abstract: Prostate cancer is a kind of male malignancy. Recently, a large number of studies have reported many potential biomarkers for the diagnosis and prognosis of prostate cancer. In this literature review, we have collected a number of potential biomarkers for prostate cancer reported in the last 5 years. Among them, some are undergoing Phase III clinical trials, and others have been approved by the US Food and Drug Administration. However, most are still in the period of basic research. The review will contribute to future research to find the biomarkers to guide clinicians to make personalized treatment decisions for each prostate cancer patient.

Keywords: lncRNAs, microRNAs, fusion gene, TMPRSS2-ERG, methylation

Plain language summary

Men have a unique malignancy, prostate cancer. Prostate cancer can be dangerous to men. Doctors and scientists have done a lot of research to detect prostate cancer. In this article, we have summarized the suggestive substances found over the years. Doctors can tell if a patient has prostate cancer by examining these substances. Some of these substances are valuable and some of them are in experiment stages. We put them all together in order to better serve doctors and patients, to enable them to know which substances can help us identify prostate cancer.

Introduction

Prostate cancer (PCa) is a leading male malignancy all over the world, with 1.1 million new cases in 2012. Globally, the incidence rates are the highest in Australia, New Zealand, North America, Northern and Western Europe, and Caribbean countries, while the mortality rates are rising in some Asian and European countries, such as Korea, China, and Russia.[1,2] In 2017, 161,360 new cases were diagnosed, and 26,730 patients were dead due to PCa in America.[3] In other words, in America, 1/6 men would develop PCa, whereas 1/35 men would die from PCa.[4]

It is well known that prostate-specific antigen (PSA) screening has increased the incidence of PCa cases at the beginning of its application in clinical routine, and the PCa incidence reached the peak after decades of the application, and now the incidence of PCa has declined from the last peak and currently has a stable slope. At present, PSA is used as a test to support the diagnosis of PCa. The patients with elevated PSA will undergo further prostate biopsy. The diagnosis of PCa is usually made by biopsy outcome and histologic evaluation. The tissues obtained from biopsy or surgical resection will be examined by pathologists to observe cell morphology, organization arrangement, and to detect the expression levels of a variety of proteins using immunohistochemistry. In addition, we have other tools, such as digital rectal examination (DRE) and magnetic resonance imaging. Imaging has more value in the diagnosis of

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aggressive or metastatic PCa, and is more commonly used for tumor staging.

Although compared with the past, the patient's diagnostic and survival rates are greatly improved, following the development of technology and science. Nowadays we are thoroughly looking forward to more sensitive and specific biomarkers in favor of accurate diagnosis and the individualized treatment for PCa. Moreover, it is also very important to find biomarkers to distinguish aggressive from indolent PCa. In the review, we used the search terms "prostate cancer" and "biomarker" to screen literatures in PubMed and CNKI databases, and searched nearly 100 related studies. We studied these literatures carefully, and relevant data were extracted and summarized in this review and Table 1. Among them, some biomarkers were already used in commercial kits, but more molecules with potential to become markers

Table 1 The list of the biomarkers for prostate cancer

Name	Full name	Predictive value	Ref	Application value
PSA	Prostate-specific antigen	PSA was used to assess patients' response to treatments, and to predict recurrence in the whole stages of PCa progression	5–7	PSA was used for dynamic monitoring recurrence after initial treatment (FDA, 1986). PSA was used in the clinic for early diagnosis of PCa (FDA, 1994). PSA testing was used in high-risk populations (the US Preventative Services Task Force, 2012)
Long noncoding RNA				
PCA3	Prostate cancer antigen 3	The PCA3 screening might have potential as a second-line test used in men with high PSA levels. A commercially available assay combining serum PSA with urinary PCA3 and TMPRSS2-ERG provided a 90% specificity and 80% sensitivity in diagnosing PCa	9, 28	The PCA3 expression level was detected as a diagnostic test for PCa in these cases with a prior negative biopsy (FDA)
PCAT14	Prostate cancer-associated transcript 14	PCAT14 was highly expressed in low-grade PCa and loss of PCAT14 predicted for disease aggressiveness and recurrence	11	
MALAT-1	Metastasis-associated lung adenocarcinoma transcript 1	The MALAT-1 score was tested in a discovery phase and a multicenter validation phase. According to the decision curve analysis, using a probability threshold of 25%, the MALAT-1 model would prevent 30.2%–46.5% of unnecessary biopsies in PSA 4–10 ng/mL cohorts, without missing any high-grade cancers	12	MALAT-1 had a higher AUC compared to PSA level to predict the risk of PCa before biopsy (a multicenter clinical trial)
PCA18	Prostate cancer antigen 18	PCA18 was upregulated in PCa tissues compared to BPH samples	13	
PVT1	Plasmacytoma variant translocation 1	PVT1 exon 9 may be associated with aggressive PCa	14	
SChLAP1	Second chromosome locus associated with prostate-1	The overexpression of SChLAP1 could independently predict biochemical recurrence of PCa after RP	15, 16	
MicroRNA				
miR-34a		The expression level of miR-34a was decreased in clinical PCa samples. And miR-34a might be related with PCa progression and poor prognosis	17	

(*Continued*)

Table 1 (*Continued*)

Name	Full name	Predictive value	Ref	Application value
miR-1		miR-1 was significantly downregulated in recurrent PCa compared to nonrecurrent PCa samples. The AUC value of miR-1 for PCa recurrence was 0.885 ($P<0.001$) with the sensitivity of 0.863 and specificity of 0.889 based on ROC curve analysis	18	
miR-129		The decrease in miR-129 expression in peripheral blood mononuclear cells was significantly associated with aggressive clinical pathologic features such as histologic grade, high preoperative PSA level, pathologic stage, high Gleason score, LN metastasis, angiolymphatic invasion, biochemical recurrence	19	
miR-21		The expression of miR-21 was significantly correlated with the Gleason score, clinical stages, bone metastasis, and tumor recurrence. The sensitivity and specificity were 94.6% and 92.8%	20, 21	
miR-191		miR-191 was the most stable gene, showing the lowest degree of variation and the highest stability value in PCa urine samples	23	
let-7 family		let-7 family was downregulated in PCa urine samples compared to the controls	24	
Fusion gene				
TMPRSS2-ERG	TMPRSS2 (transmembrane protease, serine 2), ERG (ETS (erythroblast transformation-specific)-related gene)	A commercially available assay combining serum PSA with urinary PCA3 and TMPRSS2-ERG provided a 90% specificity and 80% sensitivity in diagnosing PCa	9, 27–29	
Oncogene				
AR-V7	Androgen receptor splice variant-7	Patients with metastases but without detectable AR-V7 RNA at baseline had significantly longer OS and a trend toward superior progression-free survival	30–33	
AKR1C3	Aldo-keto reductase family 1 member C3	AKR1C3 was associated with Gleason score, PSA level, and the development of CRPC	34	
ANGPTL4	Angiopoietin-like protein 4	Positive ANGPTL4 expression in the resected PCa specimens was an independent prognostic indicator of biochemical recurrence	35	
Cav-1	Caveolin-1	Baseline Cav-1 was a significant predictor for risk of PCa	36	
CCL2	Chemokine (C-C motif) ligand 2	Patients with CCL2 ≥320 pg/mL had worse OSl and PCa-specific survival than those with CCL2 <320 pg/mL	37	
CLDN3	Claudin 3	CLDN3 levels were higher in patients with Gleason ≥8 tumors compared to patients with BPH and Gleason 6–7 tumors	38	

(*Continued*)

Table 1 (*Continued*)

Name	Full name	Predictive value	Ref	Application value
CRP	C-reactive protein	Patients with high serum CRP level (≥10 mg/L) had significantly worse OS than those patients with normal serum CRP level (<10 mg/L)	39	
EGFR	Epidermal growth factor receptor	Patients with EGFR-positive CTCs had a shorter OS than patients with EGFR-negative CTCs	40	
EN2	Engrailed-2	EN2 levels from the PCa and men with BPH were related to the tumor stage, Gleason score, and PSA	41	
Fuc-Hpt	Fucosylated haptoglobin	Serum Fuc-Hpt levels were significantly associated with Gleason score and biochemical recurrence, but not PSA levels	42	
GOAT	Ghrelin O-acyltransferase	GOAT levels in PCa patients correlated with aggressiveness and metabolic conditions. GOAT might discriminate PCa at the tissue/plasma/urine level with high sensitivity/specificity, particularly in nondiabetic individuals	43	
HOXB13	Homeobox B13	HOXB13 is overexpressed during malignant progression of the prostatic tissue and suspected to contribute in the pathogenesis of the prostate gland	44	
MIC-1	Macrophage inhibitory cytokine 1	MIC-1 concentration in serum was elevated in PCa patients compared to normal and biopsy-negative individuals	45	
NF-κB	Nuclear factor-kappa B p65	There was a significant association between an increase in the nuclear frequency of NF-κB p65 and Gleason score, and development of metastases	46	
NGF	Nerve growth factor	Urinary NGF may be a biomarker for higher-grade PCa	47	
NPY	Neuropeptide-Y	The combination of NPY and PSA had 81.5% sensitivity and 82.2% specificity for PCa diagnosis	48	
OLFM4	Olfactomedin-4	Levels of circulating OLM4 were significantly higher in patients with cancers than in healthy subjects	49	
OX	Oxytocin	The levels of OX and its receptor in serum were significantly increased in PCa patients compared to the non-carcinoma individuals	50	
PPM1D	Protein phosphatase magnesium-dependent 1 delta	PPM1D expression was positively correlated with Gleason score, T stage, and LN status. Kaplan–Meier curve analysis showed that patients with positive PPM1D expression had shorter RFS and OS	51	
PSCA	Prostate stem cell antigen	PSCA was upregulated in PCa samples	52	
PSGR	Prostate-specific G-protein-coupled receptor	PSGR may be a potential PCa biomarker and regulator of PCa invasion and inflammation	53	

(*Continued*)

Table 1 (*Continued*)

Name	Full name	Predictive value	Ref	Application value
PTK7	Protein tyrosine kinase 7	Elevated PTK7 expression was significantly associated with LN metastases, seminal vesicle invasion, tumor stage, the higher preoperative PSA, the higher Gleason score, angiolymphatic invasion, and biochemical recurrence	54	
PTX3	Pentraxin 3	PTX3 serum levels may predict PCa development	55	
S4F	Semaphorin 4F	S4F expression correlated with seminal vesicle invasion, perineural invasion, and biochemical recurrence	56	
SPINK1	Serine peptidase inhibitor, Kazal type 1	SPINK1 expression is dynamically regulated with upregulation in primary PCa and downregulation in LN metastases	57	
SPON2	Spondin-2	Serum SPON2 levels were significantly higher in patients with PCa than in healthy individuals	58	
TDRD1	Tudor domain containing 1	The expression of TDRD1 was significantly increased in ERG-positive tumors	59	
TFF3	Trefoil factor 3	Sensitivity and specificity of combined ERG and TFF3 expression in detecting PCa were 76% and 96%, respectively	60	
TK1	Thymidine kinase 1	Serum TK1 levels were significantly higher in PCa compared to blood donors	61	
TRAF2	TNF (tumor necrosis factor) receptor–associated factor 2	High expression of TRAF2 was significantly associated with PCa stage and poorer RFS	62	
TRPM4	Transient receptor potential cation channel, subfamily M, member 4	Higher staining intensity had an increased risk of biochemical recurrence compared to patients with a lower staining intensity	63	
XPO6	Exportin 6	Relatively elevated expression of XPO6 was significantly associated with poor prognosis, in particular, with rapid recurrence	64	
Tumor suppressor gene				
PTEN	Phosphatase and tensin homolog	PTEN loss was associated with high Gleason score in multiple-foci PCa cohort. These samples with homozygous deletion of PTEN were more likely to have occurrence of biochemical recurrence	9, 65	
CLU	Clusterin	Lowered serum CLU levels during custirsen treatment were predictive of longer survival in mCRPC	66	
AZGP1	Zinc-alpha 2-glycoprotein	Low/absent AZGP1 expression was an independent predictor of poor BRFS	67	Low AZGP1 expression provides independent prognostic value in PC (Phase III)
PSF1	Partner of SLD51	The PSF1 expression correlated significantly with PSA values at diagnosis, with tumor grade, and with clinical stage. Moreover, the PSF1 expression correlated significantly with OS and progression-free survival	68	

(*Continued*)

Table 1 (*Continued*)

Name	Full name	Predictive value	Ref	Application value
CCL11	Eotaxin-1	ROC analysis revealed that eotaxin-1 is a significant marker to distinguish PCa from disease-free prostate. Urine eotaxin-1 was significantly decreased in patients with PCa compared to cancer-free individuals	69	
SOX2	The SRY (sex-determining region Y)-box 2	SOX2 mRNA expression in the primary tumor was significantly associated with LN metastasis	70	
ARSB	Arylsulfatase B, N-acetylgalactosamine-4-sulfatase	In other paired normal and malignant prostate tissues, ARSB activity was significantly higher in the normal tissues	71	
MAGI2	Membrane-associated guanylate kinase inverted-2	The expression of MAGI2 mRNA was significantly downregulated in PC3, LNCaP, and DU-145 PCa cell lines, and also in clinical tumor samples. A significant correlation was observed between MAGI2 and NKX3.1 expression in tumor samples. Furthermore, the inclusion of MAGI2 in the gene panel improved the accuracy for discrimination between PCa and BPH samples with the sensitivity and specificity of 0.88 and 0.83, respectively	72	
SLC18A2	Solute carrier family 18 (vesicular monoamine), member 2	SLC18A2 transcript levels were reduced in PC and had independent prognostic value for BCR and OS	73	
ADAM19	A disintegrin and metalloproteinase 19	High levels of ADAM19 are positively associated with lower stage and reduced relapse of human PCa	74	
EFEMP1	Epidermal growth factor–containing fibulin-like extracellular matrix protein 1	Serum and urine EFEMP1 expression was significantly downregulated in patients with PCa compared to that in the control groups. The low expression of EFEMP1 was obviously affected by Gleason's score, serum PSA, pathologic stage, and LN metastasis. Moreover, there was a significant inverse correlation between EFEMP1 expression and PSA levels. The ROC curve revealed that EFEMP1 distinguished PCa patients from healthy controls	75	
SFRP1	Secreted frizzled-related protein-1	The expression of SFRP1 was correlated with the Gleason score, survival rate, and response for endocrine therapy of PCa. SFRP1 may serve as an independent predictive and prognostic factor for PCa	76	
PBX3	Pre-B-cell leukemia homeobox 3	Competing risk regression analysis revealed that high PBX3 expression was associated with slower progression to CRPC	77	
Methylated biomarker				
Hypermethylation				
PITX2, PITX3	The paired-like homeodomain transcription factors 2 and 3	PITX2 methylation discriminated between neoplastic and nonneoplastic	78	

(*Continued*)

Table 1 (*Continued*)

Name	Full name	Predictive value	Ref	Application value
		tissue in patients with PCa. PITX2 methylation significantly correlated with clinicopathologic parameters, and PITX2 hypermethylation predicted an increased risk of biochemical recurrence. PITX3 showed a significant prognostic value for BCR. PITX3 DNA methylation alone and in combination with PITX2 is a promising biomarker for the risk stratification of PCa patients		
PD-1, PD-L1	Programmed death 1, programmed death ligand 1	Normal tissue showed significantly lower levels of mPD-L1 compared to tumor tissue. High mPD-L1 in PCa was associated with BCR	79	
CDO1	Cysteine dioxygenase 1	High CDO1 methylation as continuous variable was associated with BCR	80	
GADD45a	Growth arrest and DNA-damage-inducible, alpha	Serum GADD45a methylation was significantly higher in PCa than in benign patients	81	
SLC18A2	Solute carrier family 18 (vesicular monoamine), member 2	SLC18A2 promoter hypermethylation was highly cancer-specific and associated with BCR after RP	73	
HIST1H4K	Histone cluster 1, H4k	Methylation of HIST1H4K showed significant correlation with aging, but with no other clinicopathologic characteristics	82	
cg05163709 site		The ROC analysis showed a higher AUC for cg05163709 (0.915) than prostate-specific antigen (PSA, 0.769)	83	
Hypomethylation				
TFF3	Trefoil factor 3	Sensitivity and specificity of combined ERG and TFF3 expression in detecting PCa were 76% and 96%, respectively	84	

Abbreviations: AUC, area under the curve; BRFS, biochemical recurrence-free survival; CRPC, castration-resistant prostate cancer; CTCs, circulating tumor cells; FDA, Food and Drug Administration; LN, lymph node; mCRPC, metastatic castrate-resistant prostate cancer; OS, overall survival; PCa, prostate cancer; ref, reference; RFS, recurrence-free survival; ROC, receiver operating characteristic; RP, radical prostatectomy.

were still in the laboratory research stage. We classified these molecules and looked forward for providing the researchers with a general overview of the PCa biomarkers.

PSA

PSA was the most widely used biomarker in clinical practice since the mid-80s. It was used as an adjunctive test to early screen PCa, to assess patients' response to treatments, and to predict recurrence in the whole stage of PCa progression. In 1986, the Food and Drug Administration (FDA) approved that PSA was used for dynamic monitoring recurrence after initial treatment.[5] Since then, the PCa cases in America doubled from 55/100,000 men to 110/100,000. In 1994, FDA authorized that PSA was used in the clinic for early diagnosis of PCa.[6] However, until today we still do not know how many PSA screening has reduced PCa cases and costs. The European Randomized Study of Screening for Prostate Cancer has found that clinicians must screen 1,410 men and treat 48 potential patients to prevent one person from dying of PCa.[5] In 2012, the US Preventative Services Task Force recommended that PSA testing was only used in high-risk populations.[7]

Several derivatives of PSA, including serum free PSA and PSA velocity, and the isoforms of PSA, including p2PSA, have been considered as potential biomarkers to improve the diagnostic accuracy by combining with PSA.[5] However, these auxiliary biomarkers are not PCa specific, which drastically reduces their application value. At present, PSA test is more commonly used as a screening method in clinical practice, and further diagnostic tests should be taken for

patients with elevated PSA, whereas regular re-examination should be taken for the population with PSA in the gray zone (4–10 ng/mL).

Long noncoding RNA

A lot of long noncoding RNAs (lncRNA) were identified to be associated with tumor, which might play the important roles in carcinogenesis and PCa progression. LncRNAs not only promoted cancer cells proliferation, invasion, and metastasis, but also had the potential value to become biomarkers for predicting various tumors. Several kinds of PCa-related lncRNAs are summarized as follows.

Prostate cancer antigen 3 (PCA3) was overexpressed as a second-line biomarker in PCa tissues compared with control samples. Mechanistic studies illustrated that it might regulate androgen receptor (AR) signaling to improve PCa cell survival. In addition, PCA3 level was not increased in prostatic inflammatory or hyperplasia, and its level was not associated with prostatic volume.[8] Moreover, PCA3 expression level was correlated with biopsy outcome and PCa progression (eg, tumor grade and Gleason score).[8] In 2012, FDA approved that the PCA3 expression level was detected as a diagnostic test for PCa in the cases with a prior negative biopsy.[9] Patients with PCA3 score <25 were 4.56-fold more likely to have a negative biopsy than men with its score >25.[9] In 2017, PCA3 performance was compared with the European Randomized Study of Screening for Prostate Cancer risk calculator model 3 in an opportunistic screening.[10] Eight hundred thirty-eight men with a normal DRE result and PSA ≥ 3 ng/mL had the PCA3 test done. In PCA3 positive (n=301) and PCA3 negative (n=256) groups, 40.9% and 14.7% PCa were identified, respectively ($P<0.001$).[10] The false-negative cases for high-grade PCa would be reduced by 37.1%.[10] Although the PCA3 screening might have potential as a second-line test used in men with high PSA levels, the prognostic value of PCA3 score remained controversial because the cutoff value was debated. Leyten et al found that sensitivity increased from 0.68 to 0.83 when the cutoff value reduced from 35 to 25, while specificity decreased from 0.58 to 0.51.[9]

Besides, PCAT14 (prostate cancer–associated transcript 14) was a kind of PCa-related suppressive lncRNA, which was transcriptionally regulated by AR. PCAT14 was found to be downregulated in aggressive PCa, and the loss of PCAT14 might predict PCa recurrence based on the large-scale RNA-sequencing data.[11] MALAT-1 (metastasis-associated lung adenocarcinoma transcript 1) had a higher area under the curve (AUC) compared to PSA level on the basis of a multicenter clinical trial to predict the risk of PCa before biopsy. The results showed that MALAT-1 might reduce 30.2%–46.5% of unnecessary biopsies with PSA 4–10 ng/mL using the cutoff value of 25%.[12] In addition, PCA18 (prostate cancer antigen 18) was also confirmed to be PCa-specific upregulated in PCa tissues compared with benign prostatic hyperplasia (BPH) samples ($P<0.001$).[13] PVT1 (plasmacytoma variant translocation 1) exon 9 was associated with aggressive PCa.[14] SChLAP1 (second chromosome locus associated with prostate-1) was upregulated in a subtype of PCa and associated with lethal PCa. The overexpression of SChLAP1 could independently predict biochemical recurrence of PCa after radical prostatectomy (RP). Knockdown of SChLAP1 induced apoptosis and inhibited cell invasion and metastasis.[15,16]

Among various lncRNAs, PCA3 has the most promising clinical application value and can be used as a second-line biomarker to predict the results of biopsy. Other lncRNAs also have great application prospects, and most of them are still in the research stage at present.

MicroRNAs

MicroRNA (miRNA) is a kind of small noncoding RNA with 20–24 nucleotides in length, which post-transcriptionally regulates target gene expressions by binding to the 3′-UTRs of complementary mRNAs. Deregulated miRNAs were reported to play dual roles in multiple cellular pathways in a variety of solid tumors.

A study found that the expression level of miR-34a was decreased in clinical PCa samples and was related with the progression and poor prognosis of PCa, and miR-34a might regulate BCL-2, SNCA, and SCL7A5.[17] miR-1 was significantly downregulated in recurrent PCa compared to nonrecurrent PCa samples ($P<0.001$).[18] There were 78 patients in the analysis, including 27 recurrent PCa and 51 nonrecurrent PCa. The Cox proportional hazards analysis revealed that miR-1 might be the independent prognostic factor for PCa recurrence (HR: 1.86, 95% CI: 1.21–2.94; $P=0.011$). The AUC value of miR-1 was 0.885, the sensitivity was 0.863, and the specificity was 0.889 ($P<0.001$).[18] Another biochemical recurrence predictor, miR-129, was also downregulated in peripheral blood mononuclear cells (PBMC) isolated from 98 PCa patients compared to 56 matched controls ($P<0.05$).[19] The expression level of miR-129 was significantly related with many PCa clinical characteristics: PSA level ($P=0.002$), tumor stage ($P=0.011$), Gleason score ($P=0.005$), lymph node metastasis ($P=0.002$), and biochemical recurrence ($P=0.001$), and so on.[19]

The expression levels of miR-21 were upregulated in PBMC from PCa patients compared to benign control group ($P<0.05$).[20] In the study, 92 PCa patients, 85 BPH cases, and 97 healthy controls were involved. miR-21 expression level was significantly related with Gleason score, tumor stage, bone metastasis, and recurrence ($P<0.05$). Receiver operating characteristic analysis uncovered that the AUC value of miR-21 was 0.974 with 95% CI 0.956–0.993. The sensitivity and specificity were 93.5% and 92.9%, respectively. The results illustrated that the miR-21 expression level had the potential to be an independent biomarker for predicting the prognosis of PCa ($P<0.05$).[20] Egidi et al also monitored the serum level of miR-21 in 38 patients with PCa before and after RP. MiR-21 was found to be significantly increased on the fifth day after surgery, and then gradually returned to the preoperative level. These findings suggested that miR-21 might be involved in postoperative inflammatory processes.[21] Cochetti studied the serum level of miRNAs of PCa patients, and they found that seven miRNAs (let-7c, let-7e, let-7i, miR-26a-5p, miR-26b-5p, miR-18b-5p, and miR-25-3p) could distinguish PCa from BPH.[22] In addition, Egidi[23] and Guelfi[24] detected miRNAs in the urine sediments, and found the potential application value of miR-191[23] and let-7 family[24] as noninvasive biomarkers in the diagnosis of PCa.

Our group conducted a meta-analysis and a review on differentially expressed miRNAs in PCa.[25,26] In the meta-analysis, we integrated the expression profile data of miRNAs and evaluated the value of miRNAs as biomarkers of PCa.[25] In the review, we also listed a variety of miRNAs that could identify PCa and BPH/normal.[26]

TMPRSS2-ERG

In 2005, Tomlins et al first reported the gene fused between ERG (ETS (erythroblast transformation-specific)-related gene) and TMPRSS2 (transmembrane protease, serine 2) genes.[27] TMPRSS2-ERG was the PCa-specific fusion gene, and there was ARE in the TMPRSS2 promoter, which might be activated by androgen, while the oncogene ERG was a kind of transcription factor as one member of ETS family. The fusion frequency of TMPRSS2-ERG was ~50% in Caucasian American cohorts, 31% in African American cohorts, and 18.5% in Asian cohorts. The fusion gene could regulate proliferation, differentiation, cell cycle, and so on, and played an important role in the development of PCa. TMPRSS2-ERG fusion gene was thought to be the driving factor for PCa.

In 2011, Tomlins et al found that the expression level of TMPRSS2-ERG fusion in the urine samples of biopsy and prostatectomy was associated with PCa volume and Gleason score. But TMPRSS2-ERG had not been found to be associated with long-term patient outcomes: biochemical recurrence and PCa-specific mortality. Using urinary TMPRSS2-ERG as a single marker, the test had low sensitivity but high specificity, which was very high up to 93.2%.[9] In the cohort studies, TMPRSS2-ERG fusion detection prior to biopsy was reported to avoid 35%–47% of biopsies, while to delay the diagnosis of high-grade PCa in only 1.0%–2.3%.[9] Even so, TMPRSS2-ERG fusion-based screening was limited due to its low sensitivity. So, a method to improve the discriminatory ability of TMPRSS2-ERG fusion was proposed by combining with the other urinary markers: PSA or PCA3.[28] Recently, a commercial kit might provide 90% specificity and 80% sensitivity for PCa, combined detection of serum PSA, urinary PCA3, and TMPRSS2-ERG.[28]

In 2018, our group conducted a meta-analysis on the predictive potential of TMPRSS2-ERG fusion gene. The results showed that the expression level of TMPRSS2-ERG was associated with PCa tumor stage, Gleason score, and metastasis. But it was not related with biochemical recurrence, mortality, and tumor volume. At the same time, the data showed that deletion fusion was significantly correlated with the malignant degree of PCa.[29]

Oncogene

In 2014, Antonarakis et al evaluated the expression level of androgen receptor splice variant-7 (AR-V7) in circulating tumor cells (CTCs) from metastatic castrate-resistant prostate cancer (mCRPC) patients treated by enzalutamide or abiraterone. The results demonstrated that the AR-V7 expression was associated with PCa shorter survival.[30] In 2016, Scher et al also verified that patients with AR-V7-positive CTCs had shorter radiographic progression-free survival and shorter overall survival (OS) than those with AR-V7-negative in 161 progressive mCRPC patients (HR: 0.24, 95% CI: 0.10–0.57; $P=0.035$).[31] In 2017, Saylor et al[32] got the similar conclusion. Subsequently, Conteduca et al[33] conducted the meta-analysis on the association between AR-V7 with OS or PFS in two patient cohorts: primary cohort (73 chemotherapy-naïve, 98 post-docetaxel CRPC patients) and secondary cohort (94 chemotherapy- naïve patients). The meta-analysis results suggested that AR was associated with poorer OS (primary cohort: HR: 3.98, 95% CI: 1.74–9.10; $P<0.001$ and secondary cohort: HR: 11.08, 95% CI: 2.16–56.95; $P=0.004$) and worse PFS (primary cohort: HR: 2.18, 95% CI: 1.08–4.39; $P=0.03$ and secondary cohort: HR: 4.33, 95% CI: 1.94–9.68; $P<0.001$).[33] All of the

above-mentioned studies supported that AR-V7 might be a predictive biomarker for PCa outcomes.

Besides, many proto-oncogenes are listed in Table 1. And some predictive cases of combined use of multiple oncogenes were mentioned in the discussion section. However, the oncogenes to predict and diagnose PCa have not been used in clinical practice, and a large number of experiments are still needed.

Tumor suppressor gene

Phosphatase and tensin homolog (PTEN) is a tumor suppressor gene to regulate proliferation, cell cycle, and apoptosis by a lot of downstream target genes. Among them, phosphatidylinositol-3,4,5 phosphate (PIP3) is dephosphorylated by PTEN to become phosphatidylinositol-4,5 phosphate (PIP2), then the membrane lipid is activated and released Akt kinase. In 2015, Shah et al reported that PTEN loss was associated with high Gleason score ($P<0.01$) in 194 multiple-foci PCa cohort.[65] PTEN loss was found in 36% (69) of patients. Moreover, 39% of tumor samples with hemizygous PTEN deletion was reported by Yoshimoto, while homozygous deletion was found in 5% of cases, and these samples with homozygous deletion were more likely to occur biochemical recurrence ($P=0.005$).[9]

Clusterin (CLU) is a stress-induced cytoprotective chaperone, associated with tumor stage, metastasis, and treatment resistance for some cancers. In a Phase II clinical study on custirsen, a CLU antisense oligonucleotide, custirsen as a second-line drug was evaluated in patients with mCRPC. The results showed that the lower serum CLU level indicated the longer survival period in mCRPC patients during the treatment with custirsen.[66] Moreover, in a Phase III trial, the low expression of AZGP1 (zinc-alpha 2-glycoprotein) might independently predict the shorter recurrence-free survival (HR, 1.9; 95% CI: 1.1–3.3; $P=0.02$).[67]

PSF1 (Partner of SLD51) is a kind of DNA replication factor, which was verified that its transcriptional activity was related with Gleason score ($P<0.0001$), PSA level ($P=0.0028$), and tumor stage ($P=0.0005$) in 120 PCa biopsy samples. Noteworthily, PSF1 was also associated with OS (HR: 5.5, 95% CI: 2.17–15.8; $P=0.003$) and prognosis (HR: 3.7, 95% CI: 1.28–13.43; $P=0.0143$) in 99 PCa patients.[68] Eotaxin-1 (CCL11) is an immunomodulatory chemokine attracting eosinophils. In the study using serum from 140 patients with elevated PSA levels and 20 controls, it was found that serum CCL11 levels were decreased in PCa group compared to the control ($P=0.006$), and eotaxin-1 might be a potential biomarker to distinguish PCa patients from benign prostate cases.[69]

In addition, other tumor suppressors were also confirmed to be downregulated in PCa compared to that in the healthy controls, including SOX2 (the SRY (sex-determining region Y)-box 2),[70] ARSB (arylsulfatase B, N-acetylgalactosamine-4-sulfatase) ($P<0.0001$),[71] MAGI2 (membrane-associated guanylate kinase inverted-2) ($P=0.002$),[72] SLC18A2 (solute carrier family 18 [vesicular monoamine], member 2) ($P<0.05$),[73] ADAM19 (a disintegrin and metalloproteinase 19) ($P<0.05$),[74] EFEMP1 (epidermal growth factor-containing fibulin-like extracellular matrix protein 1) ($P<0.05$),[75] and SFRP1 (secreted frizzled-related protein-1) ($P=0.016$).[76] High PBX3 (pre-B-cell leukemia homeobox 3) expression was related with slower progression to CRPC (HR: 0.18, 95% CI: 0.081–0.42; $P<0.001$).[77]

PCa-related tumor suppressor genes are the same as oncogenes. On the one hand, their application value remains to be proved; on the other hand, they are more suitable for the combined use of multiple genes to score PCa, so as to guide the clinical evaluation of the malignant degree and prognosis of PCa.

Methylated biomarker

Currently, there are more and more studies that have reported the association between DNA methylation and the carcinogenesis and progression of PCa. Aberrant DNA methylation of cancer-related genes plays an important role to regulate various kinds of signal pathways. So hypermethylated genes seem to be potential biomarkers, which may help to distinguish aggressive PCa from PCa without obvious clinical symptoms.

ConfirmMDx is a kind of assay analyzing DNA methylation patterns of several key tumor suppressors, such as glutathione S-transferase pi 1 (GSTP1), Ras association (RalGDS/AF-6) domain family member 1 (RASSF1), and adenomatosis polyposis coli (APC).[9] Among them, GSTP1 participates in detoxification, RASSF1 regulates cell cycle, and APC participates in apoptosis, cell migration, and adhesion.[9] In addition, hypermethylation of PITX2 (the paired-like homeodomain transcription factor 2) and PITX3 (paired-like homeodomain transcription factor 3) were also powerful predictors for PCa patients, which might discriminate neoplastic and nonneoplastic prostate tissues ($P<0.001$), and predict the risk of biochemical recurrence (HR: 2.56, 95% CI: 1.44–4.54; $P=0.001$).[78] Gevensleben et al evaluated the potential of hypermethylated PD-1 (programmed death 1) and PD-L1 (programmed death ligand 1) as biomarkers in PCa. First, DNA methylation of PD-1 and PD-L1 was of lower level in normal tissue compared to tumor tissue. Secondly,

hypermethylated PD-L1 was related with biochemical recurrence (HR: 1.24, 95% CI: 1.08–1.43; P=0.002) in PCa. These results indicated that PD-L1 methylation might be a prognostic biomarker for the risk assessment of PCa patients.[79] Furthermore, the promoter methylation of CDO1 (cysteine dioxygenase 1),[80] GADD45a (growth arrest and DNA-damage-inducible, alpha),[81] SLC18A2,[73] and HIST1H4K (histone cluster 1, H4k)[82] was also evaluated as prognostic biomarkers for biochemical recurrence of PCa patients after RP. In 2015, Yao et al found six aberrant methylation sites located on the Y-chromosome in PCa tissues. Among them, the methylated site (cg05163709) could become a potential diagnostic biomarker with a high AUC (0.915).[83]

Except for hypermethylation, hypomethylation of trefoil factor 3 (TFF3) promoter was studied as a PCa biomarker in 292 RP patients and another 498 PCa cases by quantitative methylation-specific PCR and DNA methylation arrays and RNA sequencing.[84] These results demonstrated that the hypomethylation of TFF3 promoter and its high expression were significant in PCa tissues compared to benign prostatic samples (P<0.001). Moreover, the expression level of TFF3 was associated with high ERG (P<0.001), high Gleason score (P<0.001), tumor stage (P<0.001), and PSA recurrence after RP (P=0.013).[84]

Both hypermethylation and hypomethylation belong to epigenetics. They are mainly used to predict the possibility of biochemical recurrence of PCa patients, and to assess the susceptibility to PCa.

Discussion

We had summarized a variety of biomarkers for PCa. Except for the molecules mentioned above, aberrant lipid metabolism markers, involving cholesteryl esters,[85] sterol regulatory element-binding protein-1, and fatty acid synthase,[86] were associated with PCa stage and Gleason score, and might distinguish PCa from benign prostate tissues. The circulating autoantibodies against tumor-associated antigens could also assist serum PSA screening to discriminate PCa from benign patients.[87,88] Single-nucleotide variant (SNV)[14] or copy number variations (CNV)[89] often led to the heterogeneity of PCa, which could be used as the characteristic of some subtype of PCa. Besides, thiosulfate[90] and miR-205[91] were reported not to be suitable as biomarkers for PCa.

In Alford's review, 12 commercially available biomarker assays were summarized, which provided urologists multifaceted information about PCa outcomes and therapeutic effects.[9] For example, SelectMDx might be used in post-DRE urine samples, involving distal-less homeobox 1, HOXC6 (homeobox C6), serum PSA level, PSA density, DRE score, age at diagnosis, and family history.[9] The oncotype DX assay measured the transcriptional levels of 17 genes by the quantitative reverse transcriptase-polymerase chain reaction, including 5 reference genes (ARF, ATP5E, CLTC, GPS1, PGK1) and 12 genes involved in the androgen pathway, cellular organization, proliferation, and stromal response.[9] Summarizing the experience of these commercially valuable kits, we found that PCa scoring combined with multiple biomarkers might be an effective method for future clinical use.

Another concern for researchers is the origin of biomarkers. Exosomes, CTCs, and cell-free-circulating-tumor DNA collected from PCa patients might be the promising source of biomarkers for evaluating PCa diagnosis and prognosis, and they could be candidate markers by themselves, such as CTC count and cell-free DNA integrity. Another advantage for these body fluid specimens is convenience and noninvasive. Among them, exosomes are vesicles that carry proteins, DNA, lipids, and metabolites, and 30–150 nm in diameter, which can come from either blood or body fluids, such as patient's urine.

In summary, a combination of multiple biomarkers should be a feasible and accurate way to assess PCa risk. In addition, a series of marker tests can provide more powerful guidance for medical decision based on the patients' different clinical and pathologic stages. Of course, a lot of laboratory and clinical experiments are still needed to achieve the goal.

Conclusion

In the review, we summarized the molecules found in recent several years, which had the potential to become biomarkers for the diagnosis and prognosis of PCa. Furthermore, we divided them into several categories, such as noncoding RNA, fusion gene, proto-oncogene, tumor suppressor gene, and gene methylation. Some of them had been applied in clinical practice, or were being developed to be used in the commercial reagent kits. However, most of the molecules were still in the laboratory research stage. More laboratory tests and clinical trials were needed.

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Disclosure

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