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An overview of prostate cancer (PCa) diagnosis: Potential role of miRNAs

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ABSTRACT

Prostate cancer is the second most frequently diagnosed cancer among men worldwide, with the estimated sixth leading cause of cancer death. Despite major advancements in clinical biology and imaging, digital rectal examination (DRE), prostate-specific antigen (PSA), and biopsies indication remain the keystone for screening. Several kits are used to detect genomic changes and non-coding RNAs in the sample. However, its indication remains controversial for screening purposes. There is an urged need for non-invasive biomarkers to implement precision medicine. Recent research shows that miRNAs have an important role in the diagnostic, prognostic, and therapeutic agents as non-invasive biomarkers. Though prostate cancer data remains controversial in other cancer types, such as breast cancer, miR-21 expression is upregulated. Here, we reported a prolonged revision of miRNAs as prostate cancer prognostic, diagnostic, and predictive tools, including data on androgen receptor (AR) signaling, epithelial-mesenchymal transition (EMT) process, and cancer stem cells (CSCs) regulation. The combined utilization of miRNAs with other tests will help patients and clinicians to select the most appropriate personalized treatment and to avoid overdiagnosis and unnecessary biopsies. Future clinical applications of our reported novel miRNAs have a substantial role in the primary diagnosis of prostate cancer to help treatment decisions.

Introduction

Prostate cancer is recognized as a major health concern in men. Prostate cancer is frequently diagnosed with a secondary malignancy in men and is the sixth leading cause of cancer-related mortality in men worldwide.1,414,259 incident cases were reported, with 375,304 deaths in 2020 [1, 2]. Prostate cancer is asymptomatic in early stages but may produce symptoms of frequent urination, nocturia, hematuria, urinary retention, and urination with pain in the pelvis at later stages. Cancer stages and grades can evaluate the status of prostate cancer. The Gleason scoring system stratifies prostate cancer risk from low to high Gleason scores based on micrographs related to apparent diffusion coefficient (ADC) in prostate cancer patients [3]. The bottleneck in diagnosing prostate cancer based on histopathological examination is high diversification. The invasive methods used in diagnosing prostate cancer have provoked scientists to unearth non-invasive procedures with more accuracy. Currently, urine and blood-based biomarkers are also used to detect prostate cancer. Digital Rectal Examination (DRE), Prostate Specific Antigen (PSA), and Transrectal Ultrasound Scan (TRUS) are commonly used diagnostic tools for prostate cancer detection. When PSA and DRE are found at a normal level, patients' chances of missing cancer are only about 10% [4]. However, this clinical test has some limitations in its implementation. PSA, DRE, and TRUS lack specificity and cannot distinguish benign from malignant prostate cancer. Prospective studies reported improved sensitivity of computer-assisted image analysis in diagnosing prostate cancer that was uncertain in previous biopsies. Despite these biomarkers' presence, the diagnosis of prostate cancer is still undisclosed due to the absence of optimal standard methods and non-specificity. There is still a dire need to develop mature non-invasive, novel biomarkers with greater sensitivity and specificity. Prostate cancer progresses very slowly, and chances of recovery are much high. It is reported that miRNAs are involved in carcinogenesis and show promising results in prostate cancer diagnosis. miRNAs are a rapidly emerging area of a current cancer diagnosis [5].

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This review will focus mainly on miRNA-based biomarkers with high specificity and sensitivity in diagnosing prostate cancer.

The dilemma of prostate cancer diagnosis

Prostate cancer is one of the cancers that has received durable interest due to its widespread in Western countries and scientific development in diagnosis and treatment. In recent decades, the mortality rate reduction from prostate cancer was associated with an increase in detection in the early stages of cancer and a decline in the proportion of cases in the advanced stages. These epidemiologic changes were linked to introducing the prostate-specific antigen (PSA) and its wide use in the detection, diagnosis, and follow-up of prostate cancer cases.

The prostate-specific antigen is a glycoprotein expressed in both cancerous and normal prostatic columnar epithelial cells, and hence it is tissue-specific and not pathology sensitive. PSA is an expression in the normal prostatic cells even more than in the cancerous prostatic cells; interestingly, in malignancy, due to the disruption of the basal cell layer and basement membrane, more PSA escapes into the circulation and can be measured in the serum in high concentration.

PSA test has been used as a screening tool to diagnose prostate cancer in the early curable stage before it reaches the advanced incurable stage. Based on this hypothesis, screening programs in many countries were established. In 2018, Dragan Ilic reported that three randomized clinical trials, including Cluster Randomized Trial (CAP 2018), The Prostate, Lung, Colorectal, and Ovarian (PLCO 2017), European Randomized Study of Screening for prostate cancer (ERSPC 2014), have shown that PSA screening results in an increase in detection of localized prostate cancer (stage I and stage II) at the expense of advanced stage (stage III and stage IV). Surprisingly, screening had no impact on overall mortality and prostate cancer-specific mortality in those three randomized clinical trials.

A screening test should be accurate with a high negative predictive value, feasible, acceptable by the community, and reasonable cost. Aside from cancer, the PSA level can be raised in many other prostatic pathologies, including benign hypertrophy, inflammation, and senility; this makes PSA's sensitivity contaminated by the other non-cancerous causes. Moreover, PSA can detect cancers that are non-lethal or clinically insignificant; such lesions were detected in autopsy series and found to have no impact on survival due to their low aggressiveness. The prostate Testing for Cancer and Treatment (ProtecT) trial has compared the effect of three treatment modalities, *i.e.*, radiotherapy, active monitoring, and surgery for localized low stage prostate cancer, and revealed a significant reduction in progression to metastatic stage within 10 years follow up after treatment, but these treatments failed to extend overall survival when compared to no treatment; thus, this study denied any survival benefit due to early treatment [6].

Overdiagnosis with clinically insignificant prostate cancer was encountered during screening programs and led to the dilemma of unnecessary biopsy and unnecessary treatment and may jeopardize the patient's life due to complications related to these pointless interventions. Complications were observed in PLCO and CAP trials due to biopsy. During the PLCO study, 75 biopsy-associated complications were observed, while three complications were reported in the CAP study. Approximately one-third of men with an increasing PSA level have prostate cancer, while the remaining two-thirds can have false-positive results. We may conclude that prostate cancer screening with PSA may be dangerous rather than useful [7].

Conventional biomarkers

Transrectal biopsy (TRB) was an important digitally directed-biopsy diagnostic test for prostate cancer in the 1970s. Nevertheless, it is not an efficient technique due to 15–46% false-negative results, and the tissue-undegrading rate is up to 38% [8]. In comparison to TRB, Transperineal biopsy (TPB) has many pros over TRB as it is clean, patient-centered, and no other broader spectrum antibody prophylaxis is required [9]. Digital Rectal Exam (DRE) and Prostate-specific Antigen (PSA) is used to detect prostate cancer that shows no symptoms previously and provides an efficient result for prostate cancer screening. DRE is used to detect the lumpy or hard areas known as nodules. At the same time, PSA is used to find abnormalities or mutations that might be suggested in the presence of prostate cancer. Neither of them is initially satisfied with the diagnostic ability as many men with elevated PSA levels have no prostate cancer symptoms, and those who have prostate cancer at the severe stage can be found with a normal level of PSA. Different factors can increase PSA levels like benign prostate hyperplasia (BPH), sexual activities, or prostate infection. Also, digital examination described the data only from the prostate glands' backside and reduced our access to analysis properly. More than 60% of patients with prostate cancer are identified as asymptomatic [10]. PSA's normal level in the human body is about considered safe is 2.6 to 4 ng/ml. People with a high PSA level go for a TRB-guided biopsies examination. PSA protein travels through the human body in two ways. The first is that it may be docked with another protein or move freely in the blood. The fPSA to tPSA ratio used in men is between 4 and 10.0 ng/ml with a normal PSA level [11].

Blood-based biomarkers

Prostate Health Index(Phi) is a mathematical expression used to improve PSA clinical performance. It is a novel approach that uses men's serum to determine the risk of prostate cancer. The phi report result can be calculated using the formula ([−2]proPSA/fPSA tPSA), which improved prostate cancer detection [12]. Phi is more specific and clinically significant than total/free PSA in diagnosing prostate cancer; a study has found [13]. 4Kscore test is used after an abnormal result of a prostate-specific antigen/digital rectal exam to check prostate cancer's aggressiveness by using four prostate-specific biomarkers. 4Kscore is another test used to assess cancer risk and categorize its stages. 4Kscore test utilizes four kallikrein peptides: fPSA, tPSA, intact PSA, and hK2; in an algorithm to assess the individual risk level percentage ($< 1\%$ to $> 95\%$). Among studies in 171 patients, a higher 4Kscore test score was strongly associated with a higher risk of prostate biopsy with a probability ($P < 0.001$) of detecting cancer [14]. A recent statistical meta-analysis study of 4Kscore evaluated the predictive accuracy of 8% to 10%, and unnecessary biopsies could be avoided by approximately 48% to 56% [15]. Circulating tumor cells initiate the metastatic process's progression with solid tumor cells. These cells circulate throughout the body with blood and are present in the bone marrow of prostate cancer patients [16]. The CellSearchTM kit (Janssen Diagnostics, USA) is an FDA-approved test and is an independent predictor of metastatic progression of prostate cancer [17]. A recent study reported that a panel of novel serum proteins is present in over 500 patients of prostate cancer. The combination of these three serum proteins, FLNA, FLNB, and KRT19 with PSA, increased the overall efficiency of prostate cancer as compared to PSA alone (AUC of PSA alone, 0.58; AUC of PSA with panel protein, 0.64). The Prediction probability of high-risk disease was (AUC of PSA alone, 0.71; AUC of PSA with FLNB, 0.81), and the prediction of benign prostatic hyperplasia *vs* cancer was (AUC of PSA alone, 0.58; AUC of PSA with FLNA, KRT19, 0.70) [18].

Urine-based biomarkers

Transcriptome analysis of the Prostate Cancer Antigen 3 (PCA3) gene shows that it is long non-coding RNA(lncRNA). The expression of PCA3 in prostate tissue was identified by using the differential display (DD3) and prostate cancer gene expression marker 1 (PCGEM1) [19]. One study showed that research was conducted on 233 men, with 226 men having RNA yield in their urine samples. PCA3 level is determined by using transcription-mediated amplification. PCA3 score of 35 was associated with a specificity of 58% to 76%, sensitivity of 58% to 82%, negative predicted value (NPV) of 87%, and positive predicted value

(PPV) of 67% to 69%. This high specificity result suggested that the PCA3 assay could have an important role in the diagnosis of prostate cancer [20]. Multiplex biomarkers are also used in the diagnosis of prostate cancer. Some multiplex biomarkers are discussed. TMPRSS2-ERG Fusion and PCA3 have high specificity but low sensitivity. However, its combination with other biomarker tests has been reported to have high specificity and sensitivity of 90% and 80%, respectively, in diagnosed prostate cancer [21]. This chromosomal rearrangement TMPRSS2-ERG fusion occurs in approximately 50% of prostate cancer, but prostate cancer regulation remains unclear [22]. SelectMDx is another multiplex non-invasive urine biomarker in which expression of two cancer-related mRNAs, Homeobox protein HOX-C6 (cell proliferation gene) and distal-less homeobox 1, DLX1 (progression gene), is measured. HOXC6 and DLX1 miRNA levels showed the best predictor for high-grade prostate cancer with an AUC of 0.90 (95% confidence interval, 0.85–0.95 [CI]). Like other traditional clinical tests, this liquid biopsy assay could reduce the number of high risks score unnecessary biopsies [23]. ExoDx prostate (IntelliScore) is a non-invasive test to detect high-grade prostate cancer (HGPC). ExoDx prostate (IntelliScore) value greater than $>$ 15.6 shows a high-risk prostate cancer condition, and the intervention is to proceed with biopsy for further analysis. EPI test result influences the intervention because it may be proceeded with biopsy or without [24, 25].

Tissue-based biomarkers

ConfirmMDx test was created to detect prostate cancer using an epigenetic assay of methylation of genes associated with prostate cancer. Intended outcomes can predict which patients have cancer occur biopsy and have a true negative biopsy and prevent a biopsy of unaffected people. This test measures the methylation level of three genes (Adenomatous Polyposis Coli, APC), Ras association domain family member 2 (RASSF2), and Glutathione S-Transferase Pi 1 (GSTP1)) associated with prostate cancer. Detection of DNA methylation in high-grade risk cancer is the most significant predictor of negative biopsies with an NPV of ~96% [26]. Oncotype DX GPS test analyses showed the overall aggressiveness of the disease by predicting prostate cancer gene activity. At the time of diagnosis, Oncotype DX GPS is the only assay used for low-risk cancer to make favorable decisions about treatment and provides a Genomic Prostate Score (GPS scale 0–100). Oncotype DX GPS test measures miRNA expression of 17 genes responsible for tumor cell growth and survival. A population of 259 shows a strong association between GPS and Prostate cancer-specific death (PCD) and metastasis. No patient with a value of GPS $\langle$ 20 developed PCD or metastasis [27]. Decipher® Prostate Test is also a genomic test used to identify a group of 22 mRNAs by measuring the expression of associated genes. A case cohort was designed to generate RNA expression of relative genes by using 1010 patients' samples after radical prostatectomy. These patients had already preoperative PSA levels$\rangle$ 20 ng/ml and Gleason 8 or greater. A 20% random sampling was taken as a subcohort to analyze patients with metastasis. 22-marker genomic classifier score was generated with available genomic data of 219 patients (AUC = 0.79). The genomic classifier was a predominant predictor of metastasis after redial prostatectomy and had a cumulative incidence of 2.4%, 6.0%, and 22.5%, with low, intermediate, and high scores, respectively (p <0.001). This study showed that genomic information could identify adverse pathological features of patients with metastasis risks [28]. ProMark (Metamark, Cambridge, USA) is a proteomic prognostic test for prostate cancer, predicting the overall aggressiveness in a patient with Gleason scores of 3 + 3 and 3 + 4. This test uses quantitative, automated image reorganization technology and multiplex immunofluorescence assay on Formalin-Fixed Paraffin-Embedded (FFPE) tissues to generate a personalized score. ProMark evaluates eight proteins panel that provides a score of 0 to 1 that predict AP [29]. A predictive value of risk assessment was studied in 381 patients with a biomarker favorable risk score of $\leq$ 0.33 and for unfavorable $>$ 0.80 that were defined on "false-positive" and "false negative" rates of 5% and 10% [30]. Some serum, urine, tissue based diagnostic biomarkers approved by FDA and CLIA have been summarized in **Table 1**.

miRNAs-based biomarkers

MicroRNAs (miRNAs) are short non-coding RNA transcripts of 17–25 nucleotides first discovered in 1993. miRNAs are known to regulate gene expression. miRNAs have an important role in cell-cell signaling, cell cycle, hormones, and apoptosis – both normal and diseased condition [37, 38]. About 2000 miRNAs in humans have been sequenced that collectively regulate the genome [39]. miRNAs are found in various biofluids, such as blood, urine, tears, saliva, and semen [40].

RNA polymerase II transcribes miRNA into ~ 80 nucleotides long pre-miRNA in the nucleus, further cleaving by Drosha RNase III and DiGeorge Syndrome Critical Region 8 (DGCR8) into shorter fragments known as pre-miRNAs [41]. The mobility of pre-miRNA from the nucleus into the cytoplasm is triggered by Exportin 5. Dicer (RNase) cleaves pre-miRNA into small 22-bp long dsRNA in the cytoplasm [42, 43]. One strand is integrated into RNA induced silencing complex (RISC) and usually targets the 3′ UTRs of mRNA [44, 45]. The targeted mRNA is degenerated and results in gene silencing [46]. Under both physiological and pathological conditions, various kinds of cells excrete miRNAs. Changes in the expression profile of miRNA are used as a potential indicator of a pathological condition. Due to the susceptibility of extracellular miRNAs to proteases, these are excreted out in protective ways via exosomes [47] and may bind with Argonaute 2 complex [48] or with high-density lipoprotein (HDL). However, the major proportion of miRNA is in the form of exosomes or binds with protein remains debatable due to variation in isolation method [49]. miRNA biogenesis is illustrated in **Fig. 1**.

Regulatory role of miRNAs in prostate cancer

MicroRNAs play an important role in gene expression by repressing transcription and translation[38]. On the other hand, miRNA has a dark side in that the abnormal expression of miRNA is associated with several ailments such as prostate cancer. Different signaling pathways involved in prostate cancer development are evasion of apoptosis, angiogenesis, cell growth, and cell differentiation. miRNAs interfere with the cell cycle and apoptosis by targeting cyclin proteins and pro-apoptotic genes [50]. Recent studies have reported that miRNAs have dual functions _ oncomiR and tsmiR _ in tumor development. miRNA contributes to cancer development by upregulating the expression of oncogenes and downregulating the tumor suppressor genes [51, 52]. miR-204–5p , miR-329–3p ,miR-127–3p are tumor suppressor miRNAs [53–55] while miR-454–3p ,miR-20a-5p and miR-32–5p are oncomiR [56]. Urologists have found that the expression profile of miRNA has revolutionized the diagnosis of prostate cancer with more specificity. miRNA expression profile enlightens the developmental lineage, cancer stage, cancer grade, and history behind cancer [57]. Previous studies have reported that the expression of miR-21 and miR-75 has risen in prostate cancer patients at early stages [58], while an aggressive state is heralded by increasing expression of miRNA-1246 [59]. miRNA contributes to prostate cancer development by controlling the genes involved in the androgen receptor signaling (AR) pathway, ectopic expression of proteins involved in the cell cycle and apoptosis, epithelial-mesenchymal transition (EMT), and Cancer stem cells (CSCs) metastasis -mostly the hallmarks of cancer described in **Table 2.** The salient mitogenic growth factor for prostate gland development is the androgen receptor (AR). Proteins act as a checkpoint and inhibitors in the cell cycle, and pro-apoptotic genes are silenced by miRNA [60, 61]. Epithelial cells acquire mesenchymal cells' properties during the EMT process and then contribute to invasion and metastasis [62, 63].

Table 1
Current approved blood, urine, and tissue-based biomarkers in prostate cancer.

Test	Molecular Markers	Rationale of the Signature	Approved as	References
Serum-based Biomarkers				
Prostate Serum Antigen (tPSA)	PSA	Primarily to screen for prostate cancer by determining specific antigens in blood	FDA*	[31]
PHI (Beckman Coulter Inc., Brea, CA, USA)	Total PSA, fPSA, proPSA	Reduced numbers of unnecessary biopsies	FDA	[32]
4 K score (OPKO lab, Miami, FL, USA)	Total PSA, fPSA, intact PSA, hK2	Risk of aggressiveness of prostate cancer	FDA, CLIAˆ-approved	[33]
Urine-based Biomarkers				
PROSTATE CANCER3 (Progensa) Hologic, Marlborough, MA, USA	PROSTATE CANCER3	Determine the risk of prostate cancer	FDA	[33]
ExoDX Prostate (Intelliscore) Exosome Diagnostics Inc., Waltham, MA, USA	Exosomal RNA (PROSTATE CANCER3, ERG, SPDEF)	Detection of high-grade prostate cancer (HGPC)	CLIA-approved	[33]
Mi-Prostate Score (Michigan Medicine, Detroit, MI, USA)	PROSTATE CANCER3 and TMPRSS2-ERG mRNA, Serum PSA	Screen prostate cancer without its symptoms (Two biomarkers)	CLIA-approved	[33]
TMPRSS2: ERG fusion gene	TMPRSS2: ERG mRNA in relation to PSA mRNA	Rebiopsy	FDA	[33]
SelectMDx (MDx Health, Irvine, CA, USA)	HOXC6, DLX1, KLK3 mRNA levels	Urine sample to measure expression of two genes	CLIA-approved	[33]
Tissue-based Biomarkers				
ConfirmMDx (MDxHealth, Irvine, CA, USA)	DNA hypermethylation (GSTP1; APC; RASSF1)	Epigenetic assay of methylation of genes involved in prostate cancer	CLIA-approved	[34]
Oncotype Dx (Genomic Health, Redwood City, CA, USA)	mRNA expression; 17 gene	Predicting adverse pathology	CLIA-approved	[35]
Decipher (GenomeDx Biosciences, San Diego, CA, USA)	mRNA expression;22 genes (cell proliferation, migration, tumor motility, androgen signaling, and immune system evasion)	Predicting metastasis	CLIA-approved	[35]
ProMark (Metamark, Cambridge, MA, USA)	Protein biomarker test (8 proteins)	Aggressiveness of prostate cancer	CLIA-approved	[36]
Prolaris (Myriad Genetics (Salt Lake City, UT)	Multi-gene expression assay (Cell cycle progression)	Aggressiveness of prostate cancer	FDA	[35]

*Food and Drug Administration (FDA), ˆClinical Laboratory Improvement Amendments (CLIA).

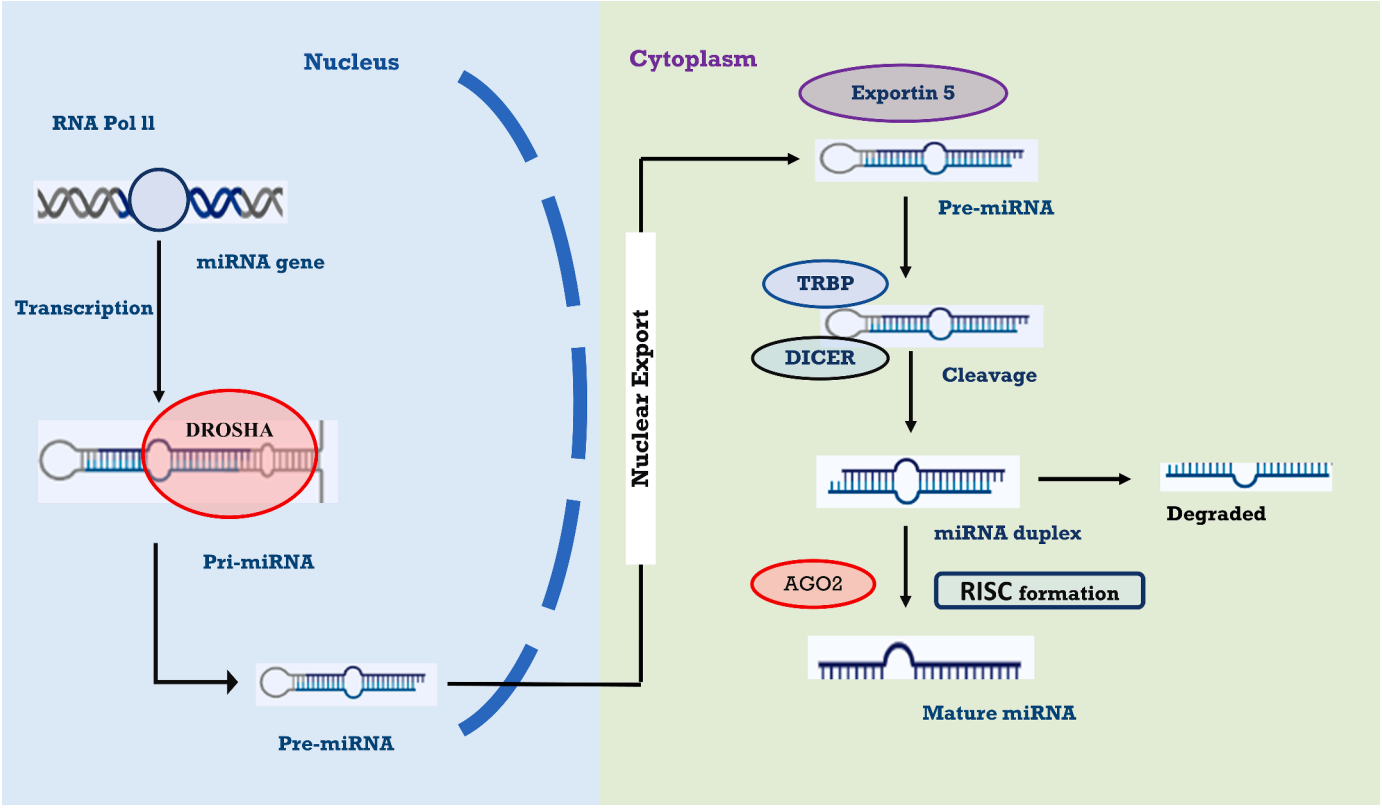

Fig. 1. miRNA biogenesis.

Androgen receptor signaling

Androgen receptor (AR) signaling plays an important role in prostate cancer's function, development, and hemostasis [64]. Androgen receptor is a type of nuclear receptor that can be activated upon binding of any androgenic hormone such as testosterone. The growth of normal prostate androgen promotes differentiation and survival. However, in

Table 2
Role of miRNAs in PCa and regulation of gene expressions in different biological pathways.

miRNAs	Up (↑)/Down (↓)	Sample Types	Target Genes	Other Biological Process	Outcome	References
Part I: miRNAs involved in triggering of cell cycle						
miR-1	↓	Tumor tissue	E2F5, CDK14, SLUG	EMT	Risk/ Prognostic	[87]
let-7a	↓	Tumor tissue/ Serum	E2F2, CCND2	Inhibit abnormal cellular proliferation	Diagnostic/ Prognostic	[88]
miR-15/ 3p	↓	Tumor tissue	TMEM97	Invasion	Diagnostic	[89]
miR-15a/16–1	↓	Tumor tissue, Serum, Exosomes	CCND1, WNT3A, BCL2	Apoptosis/ Cell survival, Proliferation	Diagnostic	[90]
miR-21	↑	Tumor tissue, Serum, Exosomes	PTEN, PDCD4, $P57^{Kip2}$	PCa progression, Apoptosis, AR signaling	Diagnostic/ Prognostic	[90]
miR-24	↓↑	Tumor tissue, Serum	CDKN1B, CDKN2A, FAF1	Reduced apoptosis	Prognostic	[91, 92]
miR-31	↓		AR, E2F1, E2F2, EXO1, FOXM1, MCM2	AR signaling	Prognostic	[93]
miR-32	↑	Tumor tissue	BTG2	Reduced Apoptosis	Diagnostic	[94]
miR-34b	↓	Tumor tissue	AKT	Inhibited cell proliferation, Colony formation	Diagnostic	[95]
miR-96	↑	Tumor tissue	FOXO1, MTSS1	Metastasis	Diagnostic / Prognostic	[96]
miR-99a	↓	Tumor tissue	NCAPG, SMARCA5, FGFR3, IGF1R	Cell proliferation	Diagnostic	[97]
miR-100	↓	Tumor tissue	MIR-100	EMT	Therapeutic	[98, 99]
miR-182	↑	Tumor tissue	ARRDC3, FOXO1	AR signaling, Metastasis	Diagnostic, Therapeutic	[100]
miR-221/222	↑	Tumor tissue, Serum	$p27^{KIP1}$/ CDKN1B	Repression of cell cycle inhibitors increases cell growth	Diagnostic	[101]
miR-449	↓	Tumor tissue	HDAC-1	–	Diagnostic	[102]
Part II: miRNAs involved in epithelial-mesenchymal transition (EMT)						
miR-1	↓	Tumor tissue	E2F5, CDK14, SLUG	Cell cycle	Risk/ Prognostic	[87]
miR-100	↓	Tumor tissue	MIR-100	Cell cycle	Therapeutic	[98, 99]
miR-200 Family	↓	Tumor tissue, Serum, Exosomes	ZEB1, ZEB2, PDGF-D, SLUG	–	Diagnostic/ Prognostic	[103]
miR-375	↑	Serum, Urine, Exosomes	SEC23A, YAP1	Cell proliferation, Stimulates cell proliferation	Prognostic/ Therapeutic	[104]
miR-940	↓	Tumor tissue	MIEN1	–	Diagnostic/ Prognostic	[105]
Part III: miRNAs involved in apoptosis						
miR-15a/16–1	↓	Tumor tissue, Serum, Exosomes	CCND1, WNT3A, BCL2	Cell cycle/ Cell survival, Proliferation	Diagnostic	[90]
miR-18a	↑	Tumor tissue	STK4	Cell survival, Proliferation	Prognostic/ Therapeutic	[106, 107]
miR-21	↑	Tumor tissue, Serum, Exosomes	PTEN, PDCD4, $P57^{Kip2}$	PCa progression/ Cell cycle, AR signaling	Diagnostic/ Prognostic	[90]
miR-24	↓↑	Tumor tissue, Serum	CDKN1B, CDKN2A, FAF1	Reduced apoptosis/ Cell cycle	Prognostic	[91, 92]
miR-125b	↓	Tumor tissue	P53, BBC3, BAK1	Loss of cell cycle checkpoint results in increased cell growth	Therapeutic	[108]
miR-133b	↓	Tumor tissue	FAIM	Tumorigenesis	Diagnostic	[109]
miR-185	↓	Tumor tissue	BRD8 ISO2, SREBP-1, SREBP-2	AR signaling, Inhibited tumorigenicity	Therapeutic	[110]
miR-205	↓	Tumor tissue, Urine	c-SRC, BCL2, AR, ZEB2, PKCε	Cell proliferation, AR signaling, EMT	Risk/ Diagnostic	[111]
Part IV: miRNAs involved in cell proliferation						
let-7a	↓	Tumor tissue/ Serum	E2F2, CCND2	Inhibit abnormal cellular proliferation/ Cell cycle	Diagnostic/ Prognostic	[88]
let-7b	↓	Tumor tissue	HMGA1	Tumor suppressor	Prognostic	[106]
let-7c	↓	Tumor tissue, Plasma	C-MYC	AR signaling/ PCa proliferation	Prognostic/ Diagnostic	[112]
miR-17	↑	Tumor tissue	STAT3, BCL2	Inhibited LNCaP cell proliferation/ Induced cell apoptosis	Prognostic/ Diagnostic	[113]
miR-18a	↑	Tumor tissue	STK4	Apoptosis/ Cell survival	Prognostic/ Therapeutic	[106, 107]
miR-21	↑	Tumor tissue, Serum, Exosomes	PTEN, PDCD4, $P57^{Kip2}$	PCa progression/ Cell cycle, Apoptosis, AR signaling	Diagnostic/ Prognostic	[90]
miR-27a	↑	Tumor tissue	ABCA1, PDS5B	–	Diagnostic/ Prognostic	[114]
miR-27b	↓↑	Tumor tissue	PI3K, AKT, p21	PCa progression	Diagnostic/ Prognostic	[94] [115],
miR-34b	↓	Tumor tissue	AKT	Cell cycle, Inhibited cell proliferation, Colony formation	Diagnostic	[95]
miR-92a	↑	Tumor tissue, Serum, Exosomes	E2F2, RRM2, PKMYT1	Tumor progression	Prognostic, Therapeutic	[116, 94, 117]
miR-93	↑	Tumor tissue, Serum	TGFBR2, ITGB8, and LATS2	Invasion	Prognostic, Therapeutic	[118]
miR-95	↑	Tumor tissue, Exosomes	JUNB	Tumor progression	Therapeutic	[94, 119]

(*continued on next page*)

Table 2 (*continued*)

miRNAs	Up (↑)/Down (↓)	Sample Types	Target Genes	Other Biological Process	Outcome	References
miR-99a	↓	Tumor tissue	NCAPG, SMARCA5, FGFR3, IGF1R	Cell cycle	Diagnostic	[97]
miR-103	↑	Tumor tissue, Serum, Exosomes	GAS5	Tumor progression and growth	Therapeutic	[94, 120]
miR-106a/ miR-106b	↑	Tumor tissue	LARP4B	Initiation of PCa	Therapeutic	[121]
miR-107	↑	Urine, Serum, Exosomes	CCNE1	–	Diagnostic / Prognostic	[116]
miR-125b	↓	Tumor tissue	P53, BBC3, BAK1	Loss of cell cycle checkpoint results in increased cell growth /Apoptosis	Therapeutic	[108]
miR-126	↓	Tumor tissue	ADAM9	Metastasis	Diagnostic, Therapeutic	[122]
miR-148a	↓	Tumor tissue	CAND1	Growth-promoting effect	Therapeutic	[123, 124]
miR-149–5p	↑	Tumor tissue	SOX2, NANOG, Oct4	–	Diagnostic	[124, 125]
miR-155	↑↓	Tumor tissue	ANX7	–	Prognostic	[94, 126]
miR-181b	↑↓	Tumor tissue	DAX-1	Progression of PCa	Diagnostic	[106, 127]
miR-195	↓	Tumor tissue	PRR11	Inhibit angiogenesis	Therapeutic	[98, 128]
miR-199a-3p	↓	Tumor tissue	SMAD1	Suppress proliferation	Diagnostic, Therapeutic	[129]
miR-221/222	↑	Tumor tissue, Serum	$p27^{KIP1}$/ CDKN1B	Repression of cell cycle inhibitors increases cell growth	Diagnostic	[101]
miR-203	↓	Tumor tissue	MAP2K1, RAP1A	Inhibiting metastasis	Prognostic	[130]
miR-205	↓	Tumor tissue, Urine	c-SRC, BCL2, AR, ZEB2, PKCε	Apoptosis, AR signaling, EMT	Risk/ Diagnostic	[111]
miR-224	↓	Tumor tissue	TRIB1	Invasion, Metastasis	Prognostic	[131]
miR-375	↑	Serum, Urine, Exosomes	SEC23A, YAP1	EMT, Stimulates cell proliferation	Prognostic/ Therapeutic	[104]
miR-429	↑	Tumor tissue, Serum	$p27^{KIP1}$	Oncogenesis	Prognostic	[132]
miR-455	↓	Tumor tissue	CCR5	Suppress progression	Therapeutic	[133]
Part V: miRNAs involved in tumor suppression						
let-7b	↓	Tumor tissue	HMGA1	–	Prognostic	[106]
miR-20a	↑	Tumor tissue, Plasma, Exosomes	RRM2, PKMYT1	-	Therapeutic	[94, 117]
miR-22	↓	Tumor tissue	LAMC1	–	Diagnostic	[94, 134]
miR-23b	↓	Tumor tissue, Plasma	MAPK	–	Prognostic	[135]
miR-29a	↓	Tumor tissue	MCL1	–	Diagnostic	[94] [134],
miR-185	↓	Tumor tissue	BRD8 ISO2, SREBP-1, SREBP-2	AR signaling, Apoptosis, Inhibited tumorigenicity	Therapeutic	[110]
miR-199a-3p	↓	Tumor tissue	SMAD1	Suppress proliferation	Diagnostic, Therapeutic	[129]
Part VI: miRNAs involved in androgen receptor (AR) signaling						
miR-124	↓	Tumor tissue	AR	–	Diagnostic	[136]
miR-143/145	↓	Tumor tissue	PROM1, CD44, OCT4, C-MYC, KLF4, ZEB2, AR	CSCs, EMT, and AR signaling Inhibit bone invasion and tumorigenicity	Diagnostic	[86]
miR-182	↑	Tumor tissue	ARRDC3, FOXO1	Metastasis, Cell cycle	Diagnostic, Therapeutic	[100]
miR-185	↓	Tumor tissue	BRD8 ISO2, SREBP-1, SREBP-2	Apoptosis, Inhibited tumorigenicity	Therapeutic	[110]
miR-205	↓	Tumor tissue, Urine	c-SRC, BCL2, AR, ZEB2, PKCε	Cell proliferation, Apoptosis, EMT	Risk/ Diagnostic	[111]
Part VII: miRNAs involved in metastasis						
miR-26a	↓	Tumor tissue	LIN28B, ZCCHC11	–	Diagnostic/ Prognostic	[91]
miR-34a	↓	Tumor tissue	CD44, STMN1	Cancer stem cells (CSCs)	Prognostic, Therapeutic agent	[85, 137]
miR-96	↑	Tumor tissue	FOXO1, MTSS1	Cell cycle	Diagnostic / Prognostic	[96]
miR-126	↓	Tumor tissue	ADAM9	Proliferation	Diagnostic, Therapeutic	[122]
miR-130a	↓	Tumor tissue	DEPDC1, SEC23B	–	Therapeutic	[124, 138]
miR-141	↑↓	Tumor tissue, Serum, Exosomes	NR0B2, CD44, EZH2, Rho GTPases	Transcriptional activity in LNCaP cells/, CSCs	Diagnostic	[90, 139]
miR-150	↓	Tumor tissue	TRPM4	Inhibition of PCa metastasis	Diagnostic, Therapeutic	[106, 140]
miR-182	↑	Tumor tissue	ARRDC3, FOXO1	AR signaling, Cell cycle	Diagnostic, Therapeutic	[100]
miR-203	↓	Tumor tissue	MAP2K1, RAP1A	Cell proliferation, Inhibiting metastasis	Prognostic	[130]
miR-224	↓	Tumor tissue	TRIB1	Cell proliferation, invasion	Prognostic	[131]
miR-409–3p/5p	↑	Tumor tissue	RSU1, STAG2, NPRL2	Increase in invasion	Therapeutic	[141]
Part VIII: miRNAs involved in cancer stem cells (CSCs) regulation						
miR-34a	↓	Tumor tissue	CD44, STMN1	Metastasis	Prognostic, Therapeutic agent	[85, 137]
miR-141	↑↓	Tumor tissue, Serum, Exosomes	NR0B2, CD44, EZH2, Rho GTPases	Transcriptional activity in LNCaP cells/, Metastasis	Diagnostic	[90, 139]

(*continued on next page*)

Table 2 (*continued*)

miRNAs	Up (↑)/Down (↓)	Sample Types	Target Genes	Other Biological Process	Outcome	References
miR-143/145	↓	Tumor tissue	PROM1, CD44, OCT4, C-MYC, KLF4, ZEB2, AR	EMT, and AR signaling Inhibit bone invasion and tumorigenicity	Diagnostic	[86]
miR-320	↓	Tumor tissue	CTNNB1	–	Therapeutic	[142]
miR-574	↑↓	Tumor tissue, Serum, Urine	REL	Recurrence of prostate cancer,	Prognostic/ Therapeutic	[143]

prostate cancer AR act as an inducer for uncontrolled cell growth [65]. The mechanism is still poorly understood but many studies showed that AR is repressed by miRNAs. Some findings represent that miRNAs interaction with 3′UTR of the AR gene is quite important in the formation of AR protein [66]. Another study revealed that some miRNAs like miR-30b-3p and miR-30d-5p direct regulate the transcriptional activities of AR which were identified through an AR-responsive promoter, a bioluminescent cell viability reporter assay, and protein lysate microarray (LMA) quantification of AR and PSA protein levels. As a result, miR-30b-3p and miR-30d-5p were significantly involved in the direct suppression of AR and PCa cell proliferation [67]. AR signaling is directly implicated in the progression and tumorigenesis of the prostate. In the same way, miR-346, miR-361–3p, and miR-197 inhibitors are also involved in a remarkable inhibition of AR transcriptional activity, increased apoptosis, repressing EMT, and cell proliferation [68]. Androgen deprivation therapy (ADT) is considered the first line of defense in prostate cancer patients with benign and malignant states. Many miRNAs involved in AR signaling initiate the progression of a pre-existing disease or the appearance of new metastasis in other parts of the body despite the prostate [69]. At the initial stage, prostate cancer requires a normal testosterone level for progression. However, at the Castration-resistant prostate cancer (CRPC) stage, it usually does not need prostate cancer, even growing at a deficient level of testosterone, which can be reduced by hormone therapy. So, AR signaling is directly involved in the emergence of CRPC [69]. The development of prostate cancer is linked with anomalous behavior of AR. AR activity may exacerbate due to mutation, hyperexpression, differential splicing [70–73], crosstalk between growth factors, and altered expression of coactivators and corepressors [74, 75]. Thus, miRNAs based therapeutic strategies can inhibit AR function and androgen-dependent cell growth.

Cell cycle and apoptosis

Recent evidence shows that miRNAs have demonstrated more than one-third of genes for their expression in humans involved in proliferation, invasion, tumorigenesis, differentiation, and apoptosis [76]. Several cluster miRNAs were concerned with the deregulation of the cell cycle, including miR-15a/16 and miR-221/222, miR-221–5p, miR-1266, miR-185 miR-30c, let-7a, miR-24 and miR-31. Proteins act as a checkpoint, and miRNAs silence inhibitors in the cell cycle and pro-apoptotic genes. Notably, an investigation reported that miR-1266, miR-185, and miR-30c are downregulated in prostate cancer, strongly associated with BCL2 and BCL2L1 genes (Anti-apoptotic genes) upregulation that can suppress the proliferation of tumor cells [77]. Similarly, miR-15a and miR-16 present in chromosomal region 13q14 are also responsible for deregulating the expression of WNT3A and BCL2 genes. These genes are involved in apoptosis resistance and cell proliferation [78].

Epithelial-mesenchymal transition (EMT) process

During EMT, the inclination of cancer cells can regulate the metastatic process, treatment resistance, and its progression. Epithelial cells lose their potency of cell-cell adhesion and polarity to attain mesenchymal properties to promote invasion. Transcriptional profile analysis revealed that mesenchymal-to-epithelial reverting transition [79] is enhanced in metastatic castrate-resistant prostate cancer (mCRPC) clinical samples that were performed with the help of reversible models of EMT [80]. The EMT is a complex and trans-differentiation process that underlies the alteration of epithelial cell phenotype to mesenchymal cells in a more motile state. Several signaling pathways and membrane proteins like Cadherin, TGF-β, and exocysts are involved in cancer development by EMT [54].

MicroRNAs play a significant role and have been reported to influence prostate cancer in the EMT process. MiRNAs controlled the prostate cancer EMT by multiple mechanisms by regulating key signaling pathways or repressing single or multiple EMT transcriptional factors (EMT-TFs) [81]. EMT pathway also facilitates tissue remodeling during embryo development. Five members of the miRNA-200 family, including miR-200a, miR-200b, miR-200c, miR-141, and miR-429, were downregulated during the EMT pathway. Enforced expression of miRNA-200 can induce EMT to target ZEB1 and SIP1 [82].

Cancer stem cells (CSCs) regulation

CSCs are a family of cancer cells with stem-like properties that can differentiate, renew, and tolerate treatments such as antimitotic agents. A better understanding of CSCs immunological properties can help induce novel immunologic approaches targeting CSCs to reduce tumor diseases [83]. MicroRNAs regulate both CSCs and normal stem cells, but miRNAs dysregulate the process of tumorigenesis [84]. MiR-34a (a p53 target) acts as a key negative regulator of CD44+ in prostate cancer cells and establishes a strong therapeutic agent against prostate CSCs [85]. Furthermore, miR143 and miR-145 suppressed colony formation of PC-3 cells from prostate cancer bone metastasis by inhibiting CSCs properties of PC-3 cancer [86].

Interplay between exosomes and prostate cancer

MicroRNAs are released in the form of exosomes by both normal and cancerous cells present in biofluids. Exosomes are small extracellular vesicles of 40–100 nm in size derived from the plasma membrane of the parent cell containing DNA, mRNA, miRNAs [144], proteins, and enzymes. Exosomes act as a carrier in cellular communication. These membrane vesicles transfer their cargoes (DNA, miRNA, and proteins) into distant recipient cells. Tumor cells produce more exosome volume than normal cells [145–148]. Exosomes make the recipient cell retain a cancerous phenotype by modulating biological pathways. Exosomes enable the cells to evade apoptosis by inhibiting pro-apoptotic genes and undergo cell division without checkpoints [149]. In 2014, it was reported that prostate tumor cells escape from immune control because exosomes downregulate the expression of receptors present on immune cells. Exosomes derived from prostate tumor cells possess an NKG2D ligand that suppresses the expression of NKG2D receptors present on NK cells and T-helper cells [150]. In the PC3 cell line, exosomes transfer its protein part integrin β4 into prostate tumor cells, promoting metastasis and invasion [151]. Exosomes increase invasion and metastasis in cancer cells by triggering epithelial-mesenchymal transition (EMT).

Exosomes released from prostate cells under hypoxia consist of more biomolecules that allow the cancer cells to undergo metastasis and invasion [152, 153]. Genetic contents and proteins present within exosomes are responsible for developing drug resistance in cancer cells [63]. The miRNA biomarkers play an important role in non-invasive biomarkers for cancer. Standardized and well-established parameters are required for miRNA to detect cancer reoccurrence and stages [154].

MicroRNAs are virtually linked with about 60% of protein-coding genes that may be regulated by miRNA activity, and all biochemical processes also include cancer progression. Several methods and protocols can detect the presence of miRNAs in the sample. Here, we just describe a schematic representation **Fig. 2.**

Exosomal miRNAs expressions in urine and blood for prostate cancer diagnosis

MicroRNAs present within exosomes has shown promising results in the diagnosis of prostate cancer with the ability to distinguish prostate cancer from benign prostatic hyperplasia (BPH). Exosomes are extracted from blood (plasma/serum) and urine. Exosomes are isolated from urine in prostate cancer because of their characteristic resemblance to urological cancer.

The expression profile of miRNA in prostate cancer patients is different as compared to control, and this attribute makes miRNA to be used as a diagnostic marker. The expression of miR-196a-5p and miR-501–3p was examined by sequestering exosomes from urine samples of a prostate cancer patient by ultracentrifugation. The sample was taken from prostate cancer patients ($n = 20$) and healthy individuals ($n = 9$). Studies have shown a significant decrease in the expression of miR-196a-5p and miR-501–3p in prostate cancer patients [155, 156]. Wani et al. reported miR-2909 in urine samples as a diagnostic tool because their level was found to rise in prostate cancer samples ($n = 90$) as compared to control subjects BPH ($n = 10$), healthy individuals ($n = 50$) [157]. The expression profile of miR-21, miR-574, and miR-141 is used to diagnose prostate carcinoma sequestered from urine exosomes using a lectin-based agglutination method. Increased expression of miR-21, miR-574, and miR-141 was observed in the initial stages of prostate cancer in prostate cancer patients ($n = 35$). These miRNAs are unique to catching prostate cancer at earlier stages [158]. Recent studies have shown that miR-21, miR-375, and let-7c are overexpressed in prostate cancer cells and associated with tumor progression and can be used as a model indicator in the diagnosis of prostate cancer. The expression of miR-21, miR-375, let-7c was analyzed in prostate cancer patient ($n = 52$) and control subjects($n = 10$).Urinary exosomes were extracted by ultracentrifugation [159]. Some miRNAs as diagnostic biomarkers are isolated from plasma and serum. Upregulation of miR-1246 in high-grade cancer makes it a highly specific biomarker. This biomarker can distinguish indolent from a lethal state with a positive predictive value. Serum was used to extract miR-1246 [59]. miR-141 functions as a tumor suppressor in several cancers, such as pancreatic cancer-promoting prostate cancer [160]. The level of miR-141 is being increased in serum with prostate cancer but remains unchanged in healthy patients. miR-141 is known to be associated with metastasis. The expression of miR-141 was evaluated in the discovery cohort, consisting of a prostate cancer patient ($n = 20$), a control group of BPH patients ($n = 20$), and healthy donors ($n = 20$) [63, 161]. miR-1290 and miR-375 both are used as predictive biomarkers in patients with Castration-resistant prostate cancer (CRPC) [162].

miRNAs used as clinical, diagnostic, and predictive biomarkers

MicroRNAs are directly involved in the pathogenesis of cancer. Due to this, miRNAs have a potential role as a diagnostic, predictive, prognostic, pharmacogenomic, and therapeutic biomarkers for both metastatic and primary cancers [163], as mentioned in **Fig. 3.** The use of miRNA is advantageous because it can be extracted from small volume samples and formalin-fixed tissues. miRNA present within exosomes has shown promising results in the diagnosis of prostate cancer with the ability to distinguish prostate cancer from benign prostatic hyperplasia (BPH). Exosomes are extracted from blood (plasma/ serum) and urine. Overall, different expression patterns and estimation profiles may help improve the management of prostate cancer. Besides this, miRNAs can be detected in different body fluids like serum and urine.

Gleason score, PSA level, and clinical stage provide current parameters for the diagnosis of prostate cancer, but beyond these parameters, miRNAs have essential information. The combination of both will improve clinicopathological parameters for diagnostic and prognostic effectiveness. Moreover, previous data suggest that some miRNAs groups have a potential role in diagnosis. A study among 20 patients

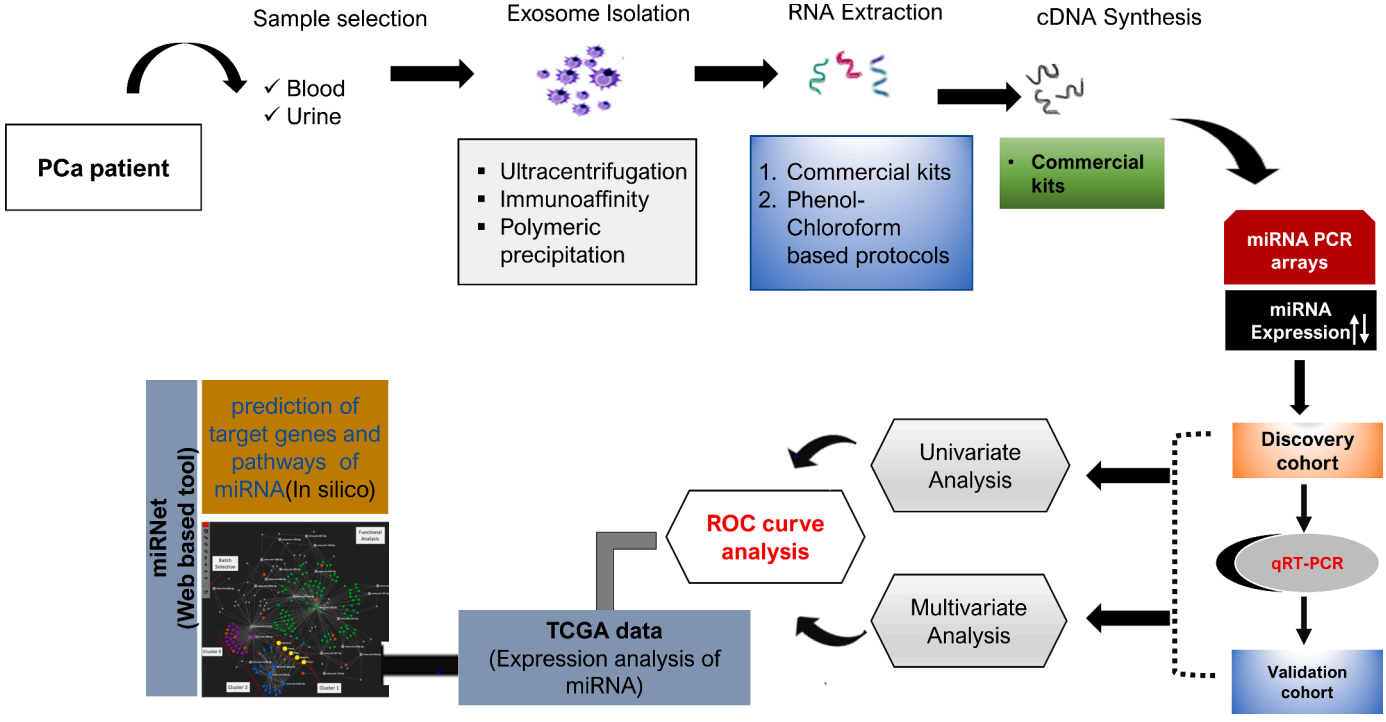

Fig. 2. Schematic representation of methodology to detect the diagnostic significance of miRNAs and in silico prediction of target genes and pathways analysis using web base tool and functional and expression analysis of miRNA using TCGA data.

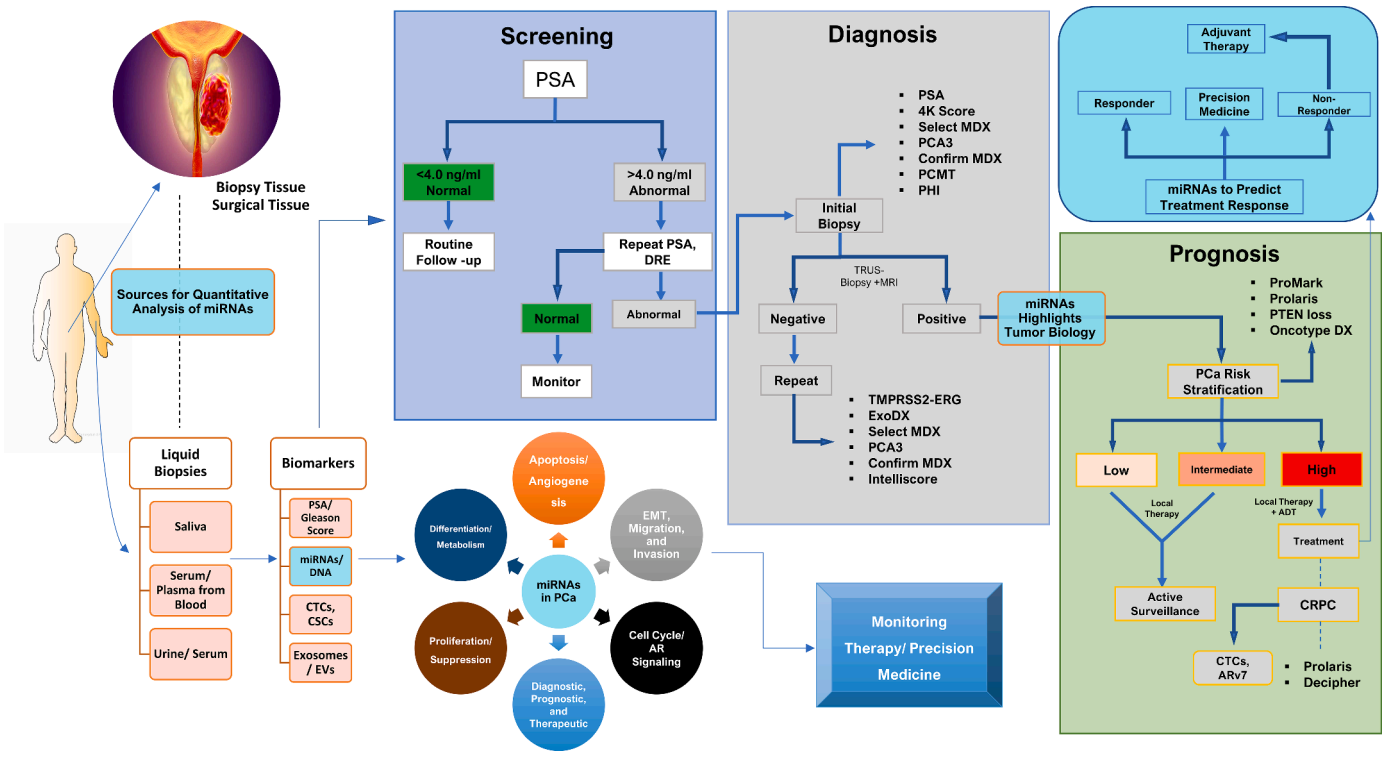

Fig. 3. Diagnostic and Prognostic biomarkers for prostate cancer management.

with a mean PSA of 21.3 ng/ml and a mean age of 68.6 years, which included eight healthy person controls, shows a group of miRNAs (miR-106b, miR-141–3p, miR-21, and miR-375). These miRNAs extracted from serum and were quantified by qRT-PCR with relative expression were increased in prostate cancer respective to healthy control [164]. These biomarkers can reduce the limitations of currently available diagnostic methods. Similarly, another study shows that the level of miR-141 increases in serum with prostate cancer but remains unchanged in healthy patients. miR-141 is known to be associated with metastasis [161].

Diagnostic tests concerned with miRNA, miRview™mets was the first test used to find the exact source of tumor cells based on miRNAs. In the first generation, this test studies a panel of 48-miRNAs in tissue measured by qPCR, which differentiated 25 different types of tumors. In the second generation, miRview mets2 test increases the number to 64-miRNA panels with 49 types of tumors [165]. However, until now, there is no diagnostic or prognostic test discovered that is only based on the detection of miRNA in body fluid.

Besides diagnostic, several studies on miRNAs expression in cancer tissue signatures have shown that it has been strongly associated with prognosis. Cuzick et al. studied the prognostic value of miRNAs expression from 31-genes involved in cell cycle progression with qRT-PCR. This study provides strong evidence between cell cycle progression and PSA level as a predictive prognostic marker that could have been used for finding treatment for patients [166]. miR-1290 and miR-375 are both used as predictive biomarkers in patients with Castration-resistant prostate cancer (CRPC) [162]. Moreover, Penney et al. assessed that expression of a 157-gene signature might improve our understanding of the tumor's de-differentiation process. It can predict Gleason score and relative lethality risk for guiding therapy decisions to improve results and reduce overtreatment [167]. Both miR 182–5p and miR-375–3p in plasma of patients were also found to be prognostic and screening biomarkers for prostate cancer [168].

Discussion

In recent years, liquid biopsy has gained a lot of attention for investigation of circulating tumor DNA, RNA, or microRNAs (miRNAs) in minimal invasive tests. miRNAs also have capability to overcome therapy resistance problem in PCa by targeting androgen receptors. For example, drug resistance that target AR ligand binding domain (LBD) is becoming a big clinical problem. So, novel therapeutics such as based on miRNAs that target AR gene regulation and suppress AR through non-LBD-mediated mechanisms will be important [68]. The important thing is the identification of specific miRNA that trigger a specific tumor-driving pathway.

Recent studies have reported that miRNAs have dual functions–oncomiR and tsmiR in tumor development. miRNA contributes to cancer development by upregulating the expression of oncogenes and downregulating the tumor suppressor genes. Despite the potential role of miRNAs in diagnostics, prognostics, and therapeutics as biomarkers for identification, disease monitoring progression, and therapy response for many human pathological conditions, there is still a lack of methodology for detecting miRNAs. Many factors are involved in the human body that can enhance the level of miRNA. Hemolysis, cell blood contamination, and platelet activation can also change the level of miRNAs in blood serum [169]. RNA extraction and storage are other significant issues that can directly influence quality. Many protocols have been proposed for miRNAs extraction in human diseases, but huge variations can impact RNA quality.

The first miRNA-based therapy to be used in clinical trials was MRX34, synthesized after the modification of miR-34a that is responsible to regulate the 24 identified oncogenes involving AR [170]. SMARTICLES liposome technology was used to deliver MRX34 in phase I of the clinical trial (NCT01829971), which provided a piece of attractive evidence for the treatment of cancer by using miRNA but was unsuccessful due to major side effects [171]. Contrarily, the FDA approved long non-coding RNA (lncRNA) PCA3 test to be used as a diagnostic marker in urine. However, its application for evaluating androgen deprivation therapy (ADT) response in advanced PCa is limited. Other

lncRNAs, like PCAT18 and SChLAP1, can be used as biomarkers for the identification of metastatic PCa.

Antisense oligonucleotides (ASOs) are another therapeutic approach that can silence genes by degrading target RNAs with RNase H. Phase II and III clinical studies for the treatment of PCa in humans had tested Bcl-2 mRNA (NCT00085228) and Clusterin mRNA (NCT01188187), but both failed due to serious adverse effects or lack of a meaningful survival benefit [65].

Lastly, data analysis is an essential step for studying identified groups of miRNAs. Normalization is one of the most provocative aspects of analysis and has no universal endogenous control. We should need further validation research on potential biomarkers. We are hopeful that advancements in science and technology could overcome these issues.

Conclusion

MicroRNAs contribute to prostate cancer development by controlling the genes involved in biological processes, ectopic expression of proteins involved in the cell cycle, and apoptosis. Deregulation of miRNAs promotes cancer progression, and this feature makes miRNA a useful diagnostic biomarker. The efficient prostate cancer screening should be sensitive enough to diagnose even asymptomatic cancer. Conventional detection can decrease cancer mortality with a lack of specificity and sensitivity. The heterogenic nature of cancer makes the detection difficult by tissue biopsy. Exosomes are the potential source of miRNA and provide a very informative platform to understand tumors' genetics. miRNA-based biomarkers are non-invasive and require a small sample volume and can differentiate indolent from aggressiveness.

The inconsistency was observed among researchers' results due to the lack of standard isolation methods for exosome isolation and differences in body fluids. There is a need to establish standard protocols and techniques to take advantage of miRNA's diagnostic and prognostic importance in reducing the prostate cancer burden worldwide. Despite these challenges, miRNA is a useful biomarker that has opened the way to diagnose prostate cancer.

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] P. Rawla, Epidemiology of prostate cancer, World J. Oncol. 10 (2) (2019) 63–89.
[2] H. Sung, et al., Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J. Clin. 71 (3) (2021) 209–249.
[3] A. Surov, H.J. Meyer, A. Wienke, Correlations between apparent diffusion coefficient and gleason score in prostate cancer: a systematic review, Eur. Urol. Oncol. 3 (4) (2020) 489–497.
[4] K. Mistry, G. Cable, Meta-analysis of prostate-specific antigen and digital rectal examination as screening tests for prostate carcinoma, J. Am. Board Fam. Pract. 16 (2) (2003) 95–101.
[5] M.S. Nicoloso, et al., MicroRNAs–the micro steering wheel of tumour metastases, Nat. Rev. Cancer 9 (4) (2009) 293–302.
[6] J.E. Shoag, et al., Reconsidering the trade-offs of prostate cancer screening, N. Engl. J. Med. 382 (25) (2020) 2465–2468.
[7] D. Ilic, et al., Prostate cancer screening with prostate-specific antigen (PSA) test: a systematic review and meta-analysis, BMJ 362 (2018) k3519.
[8] C.J. Harvey, J.P. J Richenberg, U. Patel, F. Frauscher, Applications of transrectal ultrasound in prostate cancer, Br. J. Radiol. 85 (1) (2012) S3–S17.
[9] J. Grummet, et al., Transperineal vs. transrectal biopsy in MRI targeting, Transl. Androl. Urol. 6 (3) (2017) 368–375.
[10] J.L. Descotes, Diagnosis of prostate cancer, Asian J Urol 6 (2) (2019) 129–136.
[11] P. Tang, et al., Transition zone PSA density improves the prostate cancer detection rate both in PSA 4.0-10.0 and 10.1-20.0ng/ml in Chinese men, Urol. Oncol. 31 (6) (2013) 744–748.
[12] W.J. Catalona, et al., A multicenter study of [-2]pro-prostate specific antigen combined with prostate specific antigen and free prostate specific antigen for prostate cancer detection in the 2.0 to 10.0ng/ml prostate specific antigen range, J. Urol. 185 (5) (2011) 1650–1655.
[13] A. Lepor, W.J. Catalona, S. Loeb, The prostate health index: its utility in prostate cancer detection, Urol. Clin. North Am. 43 (1) (2016) 1–6.
[14] B. Konety, et al., The 4Kscore(R) test reduces prostate biopsy rates in community and academic urology practices, Rev. Urol. 17 (4) (2015) 231–240.
[15] J.D. Voigt, et al., The Kallikrein Panel for prostate cancer screening: its economic impact, Prostate 74 (3) (2014) 250–259.
[16] C. Bettegowda, et al., Detection of circulating tumor DNA in early- and late-stage human malignancies, Sci. Transl. Med. 6 (224) (2014) 224ra24.
[17] J.S. de Bono, et al., Circulating tumor cells predict survival benefit from treatment in metastatic castration-resistant prostate cancer, Clin. Cancer Res. 14 (19) (2008) 6302–6309.
[18] S. Ravipaty, et al., Clinical validation of a serum protein panel (FLNA, FLNB and KRT19) for diagnosis of prostate cancer, J. Mol. Biomark. Diagn. 8 (2) (2017).
[19] V. Srikantan, et al., PCGEM1, a prostate-specific gene, is overexpressed in prostate cancer, Proc. Natl. Acad. Sci. U. S. A. 97 (22) (2000) 12216–12221.
[20] L.S. Marks, et al., PCA3 molecular urine assay for prostate cancer in men undergoing repeat biopsy, Urology 69 (3) (2007) 532–535.
[21] F. Sanguedolce, et al., Urine TMPRSS2: ERG fusion transcript as a biomarker for prostate cancer: literature review, Clin. Genitourin. Cancer 14 (2) (2016) 117–121.
[22] J. Yu, et al., An integrated network of androgen receptor, polycomb, and TMPRSS2-ERG gene fusions in prostate cancer progression, Cancer Cell 17 (5) (2010) 443–454.
[23] L. Van Neste, et al., Detection of high-grade prostate cancer using a urinary molecular biomarker-based risk score, Eur. Urol. 70 (5) (2016) 740–748.
[24] R. Tutrone, et al., Clinical utility of the exosome based ExoDx Prostate (IntelliScore) EPI test in men presenting for initial Biopsy with a PSA 2-10ng/mL, Prostate Cancer Prostatic Dis. 23 (4) (2020) 607–614.
[25] J. Fredsøe, et al., Diagnostic and prognostic microRNA biomarkers for prostate cancer in cell-free urine, Eur. Urol. Focus 4 (6) (2018) 825–833.
[26] L. Van Neste, et al., Risk score predicts high-grade prostate cancer in DNA-methylation positive, histopathologically negative biopsies, Prostate 76 (12) (2016) 1078–1087.
[27] S.K. Van Den Eeden, et al., A biopsy-based 17-gene genomic prostate score as a predictor of metastases and prostate cancer death in surgically treated men with clinically localized disease, Eur. Urol. 73 (1) (2018) 129–138.
[28] R.J. Karnes, et al., Validation of a genomic classifier that predicts metastasis following radical prostatectomy in an at risk patient population, J. Urol. 190 (6) (2013) 2047–2053.
[29] M. Shipitsin, et al., Identification of proteomic biomarkers predicting prostate cancer aggressiveness and lethality despite biopsy-sampling error, Br. J. Cancer 111 (6) (2014) 1201–1212.
[30] P. Blume-Jensen, et al., Development and clinical validation of an in situ biopsy-based multimarker assay for risk stratification in prostate cancer, Clin. Cancer Res. 21 (11) (2015) 2591–2600.
[31] A.R. Meyer, M.A. Gorin, First point-of-care PSA test for prostate cancer detection, Nat. Rev. Urol. 16 (6) (2019) 331–332.
[32] S. Loeb, et al., The prostate health index selectively identifies clinically significant prostate cancer, J. Urol. 193 (4) (2015) 1163–1169.
[33] E.K. Chang, A.J. Gadzinski, Y.A. Nyame, Blood and urine biomarkers in prostate cancer: are we ready for reflex testing in men with an elevated prostate-specific antigen? Asian J. Urol. 8 (4) (2021) 343–353.
[34] M.L. Blute Jr, N.A. Damaschke, D.F. Jarrard, The epigenetics of PCA diagnosis and prognosis: update on clinical applications, Curr. Opin. Urol. 25 (1) (2015) 83.
[35] V.M. Narayan, B.R. Konety, C. Warlick, Novel biomarkers for prostate cancer: an evidence-based review for use in clinical practice, Int. J. Urol. 24 (5) (2017) 352–360.
[36] S. Saini, PSA and beyond: alternative prostate cancer biomarkers, Cell. Oncol. (Dordr.) 39 (2) (2016) 97–106.
[37] R. Bayraktar, K. Van Roosbroeck, G.A. Calin, Cell-to-cell communication: microRNAs as hormones, Mol. Oncol. 11 (12) (2017) 1673–1686.
[38] M.P. Hamilton, et al., The landscape of microRNA targeting in prostate cancer defined by AGO-PAR-CLIP, Neoplasia 18 (6) (2016) 356–370.
[39] S.M. Hammond, An overview of microRNAs, Adv. Drug Deliv. Rev. 87 (2015) 3–14.
[40] B. Ortiz-Quintero, Cell-free microRNAs in blood and other body fluids, as cancer biomarkers, Cell Prolif. 49 (3) (2016) 281–303.
[41] J.N. Jingpu Wang, Beretov. Julia, et al., Exosomal microRNAs as liquid biopsy biomarkers in prostate cancer, Crit. Rev. Oncol. Hematol. (2020) 145.
[42] E. Lund, et al., Nuclear export of microRNA precursors, Science 303 (5654) (2004) 95–98.
[43] R. Yi, et al., Exportin-5 mediates the nuclear export of pre-microRNAs and short hairpin RNAs, Genes Dev. 17 (24) (2003) 3011–3016.
[44] R.C. Friedman, et al., Most mammalian mRNAs are conserved targets of microRNAs, Genome Res. 19 (1) (2009) 92–105.
[45] B.P. Lewis, C.B. Burge, D.P. Bartel, Conserved seed pairing, often flanked by adenosines, indicates that thousands of human genes are microRNA targets, Cell 120 (1) (2005) 15–20.
[46] D.P. Bartel, MicroRNAs: target recognition and regulatory functions, Cell 136 (2) (2009) 215–233.
[47] H. Valadi, et al., Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells, Nat. Cell Biol. 9 (6) (2007) 654–659.
[48] J.D. Arroyo, et al., Argonaute2 complexes carry a population of circulating microRNAs independent of vesicles in human plasma, Proc. Natl. Acad. Sci. 108 (12) (2011) 5003–5008.

[49] A. Gallo, et al., The majority of microRNAs detectable in serum and saliva is concentrated in exosomes, PLoS ONE 7 (3) (2012) e30679.
[50] M. Negrini, M.S. Nicoloso, G.A. Calin, MicroRNAs and cancer—New paradigms in molecular oncology, Curr. Opin. Cell Biol. 21 (3) (2009) 470–479.
[51] X. Liu, et al., Regulation of microRNAs by epigenetics and their interplay involved in cancer, J. Exp. Clin. Cancer Res. 32 (1) (2013) 96.
[52] T. Dalmay, D. Edwards, MicroRNAs and the hallmarks of cancer, Oncogene 25 (46) (2006) 6170–6175.
[53] J. Chen, et al., miR-127 regulates cell proliferation and senescence by targeting BCL6, PLoS ONE 8 (11) (2013) e80266.
[54] W. Bao, et al., A TrkB-STAT3-miR-204-5p regulatory circuitry controls proliferation and invasion of endometrial carcinoma cells, Mol. Cancer 12 (2013) 155.
[55] H. Yang, et al., miR-329 suppresses the growth and motility of neuroblastoma by targeting KDM1A, FEBS Lett. 588 (1) (2014) 192–197.
[56] X. Wu, et al., Down-regulation of BTG1 by miR-454-3p enhances cellular radiosensitivity in renal carcinoma cells, Radiat. Oncol. 9 (2014) 179.
[57] J. Lu, et al., MicroRNA expression profiles classify human cancers, Nature 435 (7043) (2005) 834–838.
[58] Y. Gao, et al., Analysis of circulating miRNAs 21 and 375 as potential biomarkers for early diagnosis of prostate cancer, Neoplasma 63 (4) (2016) 623–628.
[59] D. Bhagirath, et al., microRNA-1246 is an exosomal biomarker for aggressive prostate cancer, Cancer Res. 78 (7) (2018) 1833–1844.
[60] J. Cozar, et al., The role of miRNAs as biomarkers in prostate cancer, Mutat. Res./Rev. Mutat. Res. 781 (2019) 165–174.
[61] T. Chiyomaru, et al., Genistein up-regulates tumor suppressor microRNA-574-3p in prostate cancer, PLoS ONE 8 (3) (2013) e58929.
[62] V. Das, et al., The basics of epithelial–mesenchymal transition (EMT): a study from a structure, dynamics, and functional perspective, J. Cell. Physiol. 234 (9) (2019) 14535–14555.
[63] L. Min, et al., The emerging roles and clinical potential of exosomes in cancer: drug resistance, Diagn. Therapeut. Appl. Exosom. Cancer (2018) 285–311.
[64] Y. Zhou, E.C. Bolton, J.O. Jones, Androgens and androgen receptor signaling in prostate tumorigenesis, J. Mol. Endocrinol. 54 (1) (2015) R15–R29.
[65] Y. Yang, et al., Androgen receptor-related non-coding RNAs in prostate cancer, Front. Cell Dev. Biol. 9 (2021), 660853.
[66] P. Ostling, et al., Systematic analysis of microRNAs targeting the androgen receptor in prostate cancer cells, Cancer Res. 71 (5) (2011) 1956–1967.
[67] B. Kumar, et al., Identification of miR-30b-3p and miR-30d-5p as direct regulators of androgen receptor signaling in prostate cancer by complementary functional microRNA library screening, Oncotarget 7 (45) (2016) 72593–72607.
[68] C.E. Fletcher, et al., Androgen receptor-modulatory microRNAs provide insight into therapy resistance and therapeutic targets in advanced prostate cancer, Oncogene 38 (28) (2019) 5700–5724.
[69] C. Massillo, et al., Implications of microRNA dysregulation in the development of prostate cancer, Reproduction 154 (4) (2017) R81–R97.
[70] P. Koivisto, et al., Androgen receptor gene amplification: a possible molecular mechanism for androgen deprivation therapy failure in prostate cancer, Cancer Res. 57 (2) (1997) 314–319.
[71] S.M. Henshall, et al., Altered expression of androgen receptor in the malignant epithelium and adjacent stroma is associated with early relapse in prostate cancer, Cancer Res. 61 (2) (2001) 423–427.
[72] P.A. Watson, et al., Constitutively active androgen receptor splice variants expressed in castration-resistant prostate cancer require full-length androgen receptor, Proc. Natl. Acad. Sci. 107 (39) (2010) 16759–16765.
[73] S.M. Dehm, D.J. Tindall, Alternatively spliced androgen receptor variants, Endocr. Relat. Cancer 18 (5) (2011) R183.
[74] L. Léotoing, et al., Crosstalk between androgen receptor and epidermal growth factor receptor-signalling pathways: a molecular switch for epithelial cell differentiation, J. Mol. Endocrinol. 39 (2) (2007) 151–162.
[75] J.J. Voegel, et al., The coactivator TIF2 contains three nuclear receptor-binding motifs and mediates transactivation through CBP binding-dependent and-independent pathways, EMBO J. 17 (2) (1998) 507–519.
[76] P.V. Nazarov, et al., Interplay of microRNAs, transcription factors and target genes: linking dynamic expression changes to function, Nucleic. Acids. Res. 41 (5) (2013) 2817–2831.
[77] S. Ostadrahimi, et al., Downregulation of miR-1266-5P, miR-185-5P and miR-30c-2 in prostatic cancer tissue and cell lines, Oncol. Lett. 15 (5) (2018) 8157–8164.
[78] D. Bonci, et al., The miR-15a-miR-16-1 cluster controls prostate cancer by targeting multiple oncogenic activities, Nat. Med. 14 (11) (2008) 1271–1277.
[79] A.J. Vickers, et al., A panel of kallikrein marker predicts prostate cancer in a large, population-based cohort followed for 15 years without screening, Cancer Epidemiol. Biomarkers Prev. 20 (2) (2011) 255–261.
[80] N. Stylianou, et al., A molecular portrait of epithelial-mesenchymal plasticity in prostate cancer associated with clinical outcome, Oncogene 38 (7) (2019) 913–934.
[81] K. Sekhon, et al., MicroRNAs and epithelial-mesenchymal transition in prostate cancer, Oncotarget 7 (41) (2016) 67597–67611.
[82] P.A. Gregory, et al., The miR-200 family and miR-205 regulate epithelial to mesenchymal transition by targeting ZEB1 and SIP1, Nat. Cell Biol. 10 (5) (2008) 593–601.
[83] D. Zhang, D.G. Tang, K. Rycaj, Cancer stem cells: regulation programs, immunological properties and immunotherapy, Semin. Cancer Biol. 52 (Pt 2) (2018) 94–106.
[84] A. Esquela-Kerscher, F.J. Slack, Oncomirs - microRNAs with a role in cancer, Nat. Rev. Cancer 6 (4) (2006) 259–269.
[85] C. Liu, et al., The microRNA miR-34a inhibits prostate cancer stem cells and metastasis by directly repressing CD44, Nat. Med. 17 (2) (2011) 211–215.
[86] S. Huang, et al., miR-143 and miR-145 inhibit stem cell characteristics of PC-3 prostate cancer cells, Oncol. Rep. 28 (5) (2012) 1831–1837.
[87] S.M. Li, et al., The putative tumour suppressor miR-1-3p modulates prostate cancer cell aggressiveness by repressing E2F5 and PFTK1, J. Exp. Clin. Cancer Res. 37 (1) (2018) 219.
[88] Q. Dong, et al., MicroRNA let-7a inhibits proliferation of human prostate cancer cells in vitro and in vivo by targeting E2F2 and CCND2, PLoS ONE 5 (4) (2010) e10147.
[89] J. Ramalho-Carvalho, et al., A multiplatform approach identifies miR-152-3p as a common epigenetically regulated onco-suppressor in prostate cancer targeting TMEM97, Clin. Epigenet. 10 (2018) 40.
[90] Y. Hao, et al., Improvement of prostate cancer detection by integrating the PSA test with miRNA expression profiling, Cancer Invest. 29 (4) (2011) 318–324.
[91] X. Fu, et al., miR-26a enhances miRNA biogenesis by targeting Lin28B and Zcchc11 to suppress tumor growth and metastasis, Oncogene 33 (34) (2014) 4296–4306.
[92] S.M. Lynch, et al., miR-24 regulates CDKN1B/p27 expression in prostate cancer, Prostate 76 (7) (2016) 637–648.
[93] P.C. Lin, et al., Epigenetic repression of miR-31 disrupts androgen receptor homeostasis and contributes to prostate cancer progression, Cancer Res. 73 (3) (2013) 1232–1244.
[94] S.E. Jalava, et al., Androgen-regulated miR-32 targets BTG2 and is overexpressed in castration-resistant prostate cancer, Oncogene 31 (41) (2012) 4460–4471.
[95] S. Majid, et al., miRNA-34b inhibits prostate cancer through demethylation, active chromatin modifications, and AKT pathways, Clin. Cancer Res. 19 (1) (2013) 73–84.
[96] J.J. Yu, et al., miR-96 promotes cell proliferation and clonogenicity by down-regulating of FOXO1 in prostate cancer cells, Med. Oncol. 31 (4) (2014) 910.
[97] D. Wu, et al., microRNA99a inhibits cell proliferation, colony formation ability, migration and invasion by targeting fibroblast growth factor receptor 3 in prostate cancer, Mol. Med. Rep. 11 (2) (2015) 1469–1475.
[98] K.P. Porkka, et al., MicroRNA expression profiling in prostate cancer, Cancer Res. 67 (13) (2007) 6130–6135.
[99] C. Li, et al., Multiple roles of MicroRNA-100 in human cancer and its therapeutic potential, Cell. Physiol. Biochem. 37 (6) (2015) 2143–2159.
[100] J. Yao, et al., Androgen receptor regulated microRNA miR-182-5p promotes prostate cancer progression by targeting the ARRDC3/ITGB4 pathway, Biochem. Biophys. Res. Commun. 474 (1) (2016) 213–219.
[101] S. Galardi, et al., miR-221 and miR-222 expression affects the proliferation potential of human prostate carcinoma cell lines by targeting p27Kip1, J. Biol. Chem. 282 (32) (2007) 23716–23724.
[102] E.J. Noonan, et al., miR-449a targets HDAC-1 and induces growth arrest in prostate cancer, Oncogene 28 (14) (2009) 1714–1724.
[103] Y.N. Liu, et al., MiR-1 and miR-200 inhibit EMT via Slug-dependent and tumorigenesis via Slug-independent mechanisms, Oncogene 32 (3) (2013) 296–306.
[104] L.A. Selth, et al., A ZEB1-miR-375-YAP1 pathway regulates epithelial plasticity in prostate cancer, Oncogene 36 (1) (2017) 24–34.
[105] S. Rajendiran, et al., MicroRNA-940 suppresses prostate cancer migration and invasion by regulating MIEN1, Mol. Cancer 13 (2014) 250.
[106] M. Schubert, et al., Distinct microRNA expression profile in prostate cancer patients with early clinical failure and the impact of let-7 as prognostic marker in high-risk prostate cancer, PLoS ONE 8 (6) (2013) e65064.
[107] T.I. Hsu, et al., MicroRNA-18a is elevated in prostate cancer and promotes tumorigenesis through suppressing STK4 in vitro and in vivo, Oncogenesis 3 (2014) e99.
[108] X.B. Shi, et al., miR-125b promotes growth of prostate cancer xenograft tumor through targeting pro-apoptotic genes, Prostate 71 (5) (2011) 538–549.
[109] J.P. Patron, et al., MiR-133b targets antiapoptotic genes and enhances death receptor-induced apoptosis, PLoS ONE 7 (4) (2012) e35345.
[110] X. Li, et al., MicroRNA-185 and 342 inhibit tumorigenicity and induce apoptosis through blockade of the SREBP metabolic pathway in prostate cancer cells, PLoS ONE 8 (8) (2013) e70987.
[111] B. Verdoodt, et al., MicroRNA-205, a novel regulator of the anti-apoptotic protein Bcl2, is downregulated in prostate cancer, Int. J. Oncol. 43 (1) (2013) 307–314.
[112] N. Nadiminty, et al., MicroRNA let-7c suppresses androgen receptor expression and activity via regulation of Myc expression in prostate cancer cells, J. Biol. Chem. 287 (2) (2012) 1527–1537.
[113] H. Dai, et al., MiR-17 regulates prostate cancer cell proliferation and apoptosis through inhibiting JAK-STAT3 signaling pathway, Cancer Biother. Radiopharm. 33 (3) (2018) 103–109.
[114] W. Mo, et al., Identification of novel AR-targeted microRNAs mediating androgen signalling through critical pathways to regulate cell viability in prostate cancer, PLoS ONE 8 (2) (2013) e56592.
[115] T. Li, X. Sun, Y. Liu, miR-27b expression in diagnosis and evaluation prognosis of prostate cancer, Int. J. Clin. Exp. Pathol. 10 (12) (2017) 11415–11424.
[116] N.P. Hessvik, et al., Profiling of microRNAs in exosomes released from PC-3 prostate cancer cells, Biochim. Biophys. Acta 1819 (11–12) (2012) 1154–1163.
[117] J. Wei, et al., Integrative analysis of MicroRNA and gene interactions for revealing candidate signatures in prostate cancer, Front. Genet. 11 (2020) 176.

[118] J.J. Liu, X. Zhang, X.H. Wu, miR-93 promotes the growth and invasion of prostate cancer by upregulating its target genes TGFBR2, ITGB8, and LATS2, Mol. Ther. Oncolyt. 11 (2018) 14–19.
[119] H. Guan, et al., Tumor-associated macrophages promote prostate cancer progression via exosome-mediated miR-95 transfer, J. Cell. Physiol. 235 (12) (2020) 9729–9742.
[120] D. Xue, et al., LncRNA GAS5 inhibits proliferation and progression of prostate cancer by targeting miR-103 through AKT/mTOR signaling pathway, Tumour Biol. (2016).
[121] W. Yin, et al., MicroRNA106b functions as an oncogene and regulates tumor viability and metastasis by targeting LARP4B in prostate cancer, Mol. Med. Rep. 20 (2) (2019) 951–958.
[122] Y. Hua, et al., MicroRNA-126 inhibits proliferation and metastasis in prostate cancer via regulation of ADAM9, Oncol. Lett. 15 (6) (2018) 9051–9060.
[123] T. Murata, et al., miR-148a is an androgen-responsive microRNA that promotes LNCaP prostate cell growth by repressing its target CAND1 expression, Prostate Cancer Prostatic Dis. 13 (4) (2010) 356–361.
[124] M. Hart, et al., Comparative microRNA profiling of prostate carcinomas with increasing tumor stage by deep sequencing, Mol. Cancer Res. 12 (2) (2014) 250–263.
[125] T. Fujii, et al., Syndecan-1 responsive microRNA-126 and 149 regulate cell proliferation in prostate cancer, Biochem. Biophys. Res. Commun. 456 (1) (2015) 183–189.
[126] Z.K. Cai, et al., microRNA-155 promotes the proliferation of prostate cancer cells by targeting annexin 7, Mol. Med. Rep. 11 (1) (2015) 533–538.
[127] S.J. Tong, et al., microRNA-181 promotes prostate cancer cell proliferation by regulating DAX-1 expression, Exp. Ther. Med. 8 (4) (2014) 1296–1300.
[128] C. Cai, et al., miR-195 inhibits cell proliferation and angiogenesis in human prostate cancer by downregulating PRR11 expression, Oncol. Rep. 39 (4) (2018) 1658–1670.
[129] F. Qu, et al., MiR-199a-3p suppresses proliferation and invasion of prostate cancer cells by targeting Smad1, Oncotarget 8 (32) (2017) 52465–52473.
[130] J. Xiang, et al., MiR-203 down-regulates Rap1A and suppresses cell proliferation, adhesion and invasion in prostate cancer, J. Exp. Clin. Cancer Res. 34 (2015) 8.
[131] Z.Y. Lin, et al., MicroRNA-224 inhibits progression of human prostate cancer by downregulating TRIB1, Int. J. Cancer 135 (3) (2014) 541–550.
[132] Y. Ouyang, et al., Downregulation of microRNA-429 inhibits cell proliferation by targeting p27Kip1 in human prostate cancer cells, Mol. Med. Rep. 11 (2) (2015) 1435–1441.
[133] Q. Xing, et al., MiR-455-5p suppresses the progression of prostate cancer by targeting CCR5, Biomed. Res. Int. 2019 (2019), 6394784.
[134] L. Pasqualini, et al., miR-22 and miR-29a are members of the androgen receptor cistrome modulating LAMC1 and Mcl-1 in prostate cancer, Mol. Endocrinol. 29 (7) (2015) 1037–1054.
[135] S.H. Aghaee-Bakhtiari, et al., MAPK and JAK/STAT pathways targeted by miR-23a and miR-23b in prostate cancer: computational and in vitro approaches, Tumour Biol. 36 (6) (2015) 4203–4212.
[136] X.B. Shi, et al., Tumor suppressive miR-124 targets androgen receptor and inhibits proliferation of prostate cancer cells, Oncogene 32 (35) (2013) 4130–4138.
[137] B. Chakravarthi, et al., miR-34a regulates expression of the stathmin-1 oncoprotein and prostate cancer progression, Mol. Cancer Res. 16 (7) (2018) 1125–1137.
[138] J. Ramalho-Carvalho, et al., Epigenetic disruption of miR-130a promotes prostate cancer by targeting SEC23B and DEPDC1, Cancer Lett. 385 (2017) 150–159.
[139] C. Liu, et al., MicroRNA-141 suppresses prostate cancer stem cells and metastasis by targeting a cohort of pro-metastasis genes, Nat. Commun. 8 (2017) 14270.
[140] X. Hong, J.J. Yu, MicroRNA-150 suppresses epithelial-mesenchymal transition, invasion, and metastasis in prostate cancer through the TRPM4-mediated beta-catenin signaling pathway, Am. J. Physiol. Cell Physiol. 316 (4) (2019) C463–C480.
[141] S. Josson, et al., Stromal fibroblast-derived miR-409 promotes epithelial-to-mesenchymal transition and prostate tumorigenesis, Oncogene 34 (21) (2015) 2690–2699.
[142] I.S. Hsieh, et al., MicroRNA-320 suppresses the stem cell-like characteristics of prostate cancer cells by downregulating the Wnt/beta-catenin signaling pathway, Carcinogenesis 34 (3) (2013) 530–538.
[143] X. Lai, et al., Downregulation of microRNA574 in cancer stem cells causes recurrence of prostate cancer via targeting REL, Oncol. Rep. 36 (6) (2016) 3651–3656.
[144] M. Ramirez-Garrastacho, et al., Potential of miRNAs in urinary extracellular vesicles for management of active surveillance in prostate cancer patients, Br. J. Cancer 126 (3) (2022) 492–501.
[145] Y. Jia, et al., Exosome: emerging biomarker in breast cancer, Oncotarget 8 (25) (2017) 41717–41733.
[146] M. Simons, G. Raposo, Exosomes–vesicular carriers for intercellular communication, Curr. Opin. Cell Biol. 21 (4) (2009) 575–581.
[147] R. Kalluri, V.S. LeBleu, The biology, function, and biomedical applications of exosomes, Science 367 (6478) (2020).
[148] S.L. Shiao, G.C.-Y. Chu, L.W. Chung, Regulation of prostate cancer progression by the tumor microenvironment, Cancer letters 380 (1) (2016) 340–348.
[149] E. Hosseini-Beheshti, et al., Exosomes confer pro-survival signals to alter the phenotype of prostate cells in their surrounding environment, Oncotarget 7 (12) (2016) 14639.
[150] M. Lundholm, et al., Prostate tumor-derived exosomes down-regulate NKG2D expression on natural killer cells and CD8+ T cells: mechanism of immune evasion, PLoS ONE 9 (9) (2014), e108925.
[151] K. Kawakami, et al., Integrin β4 and vinculin contained in exosomes are potential markers for progression of prostate cancer associated with taxane-resistance, Int. J. Oncol. 47 (1) (2015) 384–390.
[152] L.J. Vella, The emerging role of exosomes in epithelial–mesenchymal-transition in cancer, Front. Oncol. 4 (2014) 361.
[153] A. Ramteke, et al., Exosomes secreted under hypoxia enhance invasiveness and stemness of prostate cancer cells by targeting adherens junction molecules, Mol. Carcinog. 54 (7) (2013) 554–565.
[154] M.A. Cortez, et al., MicroRNAs in body fluids–the mix of hormones and biomarkers, Nat. Rev. Clin. Oncol. 8 (8) (2011) 467–477.
[155] M. Rodríguez, et al., Identification of non-invasive miRNAs biomarkers for prostate cancer by deep sequencing analysis of urinary exosomes, Mol. Cancer 16 (1) (2017) 156.
[156] R. Bryant, et al., Changes in circulating microRNA levels associated with prostate cancer, Br. J. Cancer 106 (4) (2012) 768–774.
[157] S. Wani, et al., Urinary-exosomal miR-2909: a novel pathognomonic trait of prostate cancer severity, J. Biotechnol. 259 (2017) 135–139.
[158] R. Samsonov, et al., Lectin-induced agglutination method of urinary exosomes isolation followed by mi-RNA analysis: application for prostate cancer diagnostic, Prostate 76 (1) (2016) 68–79.
[159] L. Foj, et al., Exosomal and non-exosomal urinary miRNAs in prostate cancer detection and prognosis, Prostate 77 (6) (2017) 573–583.
[160] Z.-.M. Zhu, et al., Prognostic significance of microRNA-141 expression and its tumor suppressor function in human pancreatic ductal adenocarcinoma, Mol. Cell. Biochem. 388 (1–2) (2014) 39–49.
[161] Z. Li, et al., Exosomal microRNA-141 is upregulated in the serum of prostate cancer patients, Onco Targets Ther. 9 (2016) 139.
[162] X. Huang, et al., Exosomal miR-1290 and miR-375 as prognostic markers in castration-resistant prostate cancer, Eur. Urol. 67 (1) (2015) 33–41.
[163] Z. Lichner, et al., MicroRNA signature helps distinguish early from late biochemical failure in prostate cancer, Clin. Chem. 59 (11) (2013) 1595–1603.
[164] P. Porzycki, et al., Combination of three miRNA (miR-141, miR-21, and miR-375) as potential diagnostic tool for prostate cancer recognition, Int. Urol. Nephrol. 50 (9) (2018) 1619–1626.
[165] E. Meiri, et al., A second-generation microRNA-based assay for diagnosing tumor tissue origin, Oncologist 17 (6) (2012) 801–812.
[166] J. Cuzick, et al., Prognostic value of an RNA expression signature derived from cell cycle proliferation genes in patients with prostate cancer: a retrospective study, Lancet Oncol. 12 (3) (2011) 245–255.
[167] K.L. Penney, et al., mRNA expression signature of Gleason grade predicts lethal prostate cancer, J. Clin. Oncol. 29 (17) (2011) 2391–2396.
[168] D. Bidarra, et al., Circulating MicroRNAs as Biomarkers for Prostate Cancer Detection and Metastasis Development Prediction, Front. Oncol. 9 (2019) 900.
[169] M.B. Kirschner, et al., Haemolysis during sample preparation alters microRNA content of plasma, PLoS ONE 6 (9) (2011) e24145.
[170] A. Bouchie, First microRNA mimic enters clinic, Nat. Biotechnol. 31 (7) (2013) 577.
[171] D.S. Hong, et al., Phase 1 study of MRX34, a liposomal miR-34a mimic, in patients with advanced solid tumours, Br. J. Cancer 122 (11) (2020) 1630–1637.