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 urgent 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 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 PSA to IPSA 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 ([1−2 proPSA]/IPSA IPSA), 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: :PSA, 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 4Kcore 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 4Kcore 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 prostate hyperplasia vs cancer was (AUC of PSA alone, 0.58; AUC of PSA with FLNA, KRT19, 0.70) [18].

Urinary-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 miRNAs, Homeobox protein HOX-C6 (cell proliferation gene) and distal-less homeobox 1, DLX1 (progression gene), is measured. HOX-C6 and DLX1 mRNA 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 GS test analyses showed the overall aggressiveness of the disease by predicting prostate cancer gene activity. At the time of diagnosis, Oncotype DX GS 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 GS 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 ( 20 developed PCD or metastasis [27]. Decipher® Prostate Test is also a genomic test used to identify a group of 22 miRNAs 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 ≥ 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 radical 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 + 5 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 ≤ 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 RNAIII and DiGeorge Syndrome Critical Region 8 (DGC8R) 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 miRNA is degraded 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 extra-cellular 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 down-regulating 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 miR-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 mitochondrial 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].
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 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 (PSA)  | 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, CLIA*-approved | [33]       |
| Urine-based Biomarkers        |                   |                                            |                |            |
| PROSTATE CANCER3 (Progenia)   | PROSTATE CANCER3  | Determine the risk of prostate cancer                                                     | FDA            | [33]       |
| Hologic, Marlborough, MA, USA | Exosomal RNA (PROSTATE CANCER3, ERG, SPDEF) | Detection of high-grade prostate cancer (HGPC)                                           | CLIA-approved  | [33]       |
| EuroDX Prostate (InteliCare) Exosome Diagnostics Inc., Waltham, MA, USA | PROSTATE CANCER3 and TMPRSS2-ERG mRNA, Serum PSA | Screen prostate cancer without its symptoms (Two biomarkers) | CLIA-approv | [33]       |
| Mi-Prostate Score (Michigan Medicine, Detroit, MI, USA) | TMPRSS2: ERG mRNA in relation to PSA mRNA | Urine sample to measure expression of two genes                                           | FDA, CLIA-approv | [33]       |
| SelectMDx (MDx Health, Irvine, CA, USA) | HOXC6, DLX1, KLK3 mRNA levels | Risk of aggressiveness of prostate cancer                                                  | FDA, CLIA-approv | [33]       |
| Tissue-based Biomarkers       |                   |                                            |                |            |
| ConfirmMDx (MDxHealth, Irvine, CA, USA) | DNA hypermethylation (GSTP1; APC; RASSFL) | Epigenetic assay of methylation of genes involved in prostate cancer                      | CLIA-approv | [34]       |
| Oncotype Dx (Genomic Health, Redwood City, CA, USA) | mRNA expression; 17 gene | Predicting adverse pathology                                                               | FDA            | [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-approv | [35]       |
| ProMark (Metamark, Cambridge, MA, USA) | Protein biomarker test (8 proteins) | Deoxyribonucleic acid (DNA) methylation assay                                             | FDA            | [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), * ^Clinical Laboratory Improvement Amendments (CLIA).
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-15a/16-1 | ↓ | Tumor tissue, Serum, Exosomes | TME9MT | Invasion | Diagnostic | [89] |
| miR-21 | ↑ | Tumor tissue, Serum, Exosomes | PTEN, PDCD4, P57kip2 | PCa progression, Apoptosis, AR signaling | Diagnostic/ Prognostic | [90] |
| miR-24 | ↑ | Tumor tissue, Serum, Exosomes | CDKN1B, CDKN2A, FAF1 | Reduced apoptosis | Prognostic | [91, 92] |
| miR-31 | ↓ | Tumor tissue, Serum | 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, IGFR1 | Cell proliferation | Diagnostic | [97] |
| miR-100 | ↑ | Tumor tissue | MIR-100 | EMT | Therapeutic | [98, 99] |
| miR-182 | ↑ | Tumor tissue | ARRD3C, FOXO1 | AR signaling, Metastasis | Diagnostic, Therapeutic | [100] |
| miR-221/222 | ↑ | Tumor tissue, Serum | P27kip1/ 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, PDG-D, SLUG | – | Diagnostic/ Prognostic | [103] |
| miR-375 | ↑ | Serum, Urine, Exosomes | SEC23A, YAP1 | Cell proliferation, Stimulates cell proliferation | Therapeutic | [104] |
| miR-940 | ↓ | Tumor tissue | MIEN1 | – | Diagnostic | [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, P57kip2 | PCa progression/ Cell cycle, AR signaling | Diagnostic/ Prognostic | [90] |
| miR-24 | ↑ | Tumor tissue, Serum, Exosomes | 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, PKCz | 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 | Diagnostic/ Prognostic | [112] |
| miR-17 | ↑ | Tumor tissue | STAT3, BCL2 | Inhibited LNCaP cell proliferation/ Induced cell apoptosis | Diagnostic | [113] |
| miR-18a | ↑ | Tumor tissue | STK4 | Apoptosis/ Cell survival | Prognostic/ Therapeutic | [106, 107] |
| miR-21 | ↑ | Tumor tissue, Serum, Exosomes | PTEN, PDCD4, P57kip2 | PCa progression/ Cell cycle, Apoptosis, AR signaling | Diagnostic/ Prognostic | [90] |
| miR-27a | ↑ | Tumor tissue, Serum, Exosomes | ABCA1, PDS5B | – | Diagnostic | [114] |
| miR-27b | ↑ | Tumor tissue | PI3K, AKT, p21 | PCa progression | Diagnostic/ Prognostic | [94] [115], Diagnostic | [95] |
| miR-34b | ↓ | Tumor tissue | AKT | Cell cycle, Inhibited cell proliferation, Colony formation | Diagnostic | [95] |
| miR-92a | ↑ | Tumor tissue, Serum, Exosomes | E2F2, RR2M2, PKMYT1 | Tumor progression | Therapeutic | [116, 94, 117] |
| miR-93 | ↑ | Tumor tissue, Serum, Exosomes | TGFBR2, ITGB8, and LATS2 | Invasion | 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, Serum, Exosomes | NCAF1, SMARCA5, FGFR3, IGFR1 | 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 | [116] |
| miR-125b | ↓ | Tumor tissue | P53, BCC3, 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, NANO, 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 | – | – | – |
| Tumor tissue, Serum | ↑ | c27KIP1 / CDK11B | Repression of cell cycle inhibitors increases cell growth | Diagnostic | [101] |
| Tumor tissue | ↑ | MAP2K1, RAP1A | Inhibiting metastasis | Prognostic | [130] |
| Tumor tissue, Urine | ↑ | c-SRC, BCL2, AR, ZEB2, PKCε | Apoptosis, AR signaling, EMT | Risk/ Diagnostic | [111] |
| Tumor tissue, Urine | ↑ | TRIB1 | Invasion, Metastasis | Prognostic | [131] |
| Tumor tissue | ↑ | SEC23A, YAP1 | EMT, Stimulates cell proliferation | Prognostic/ Therapeutic | [104] |
| Tumor tissue | ↑ | p27KIP1 | Oncogenesis | Prognostic | [132] |
| Tumor tissue, Serum | ↑ | GCR5 | Suppress progression | Therapeutic | [133] |

Part V: miRNAs involved in tumor suppression

| miR-221/222 | ↑ | Tumor tissue, Serum | p27KIP1 | Repression of cell cycle inhibitors increases cell growth | Diagnostic | [94, 117] |
| miR-203 | ↑ | Tumor tissue | MAP2K1, RAP1A | Inhibiting metastasis | Prognostic | [106] |
| miR-205 | ↑ | Tumor tissue, Urine | c-SRC, BCL2, AR, ZEB2, PKCε | Apoptosis, AR signaling, EMT | Risk/ Diagnostic | [111] |
| miR-375 | ↑ | Tumor tissue | TRIB1 | Invasion, Metastasis | Prognostic | [131] |
| miR-429 | ↑ | Tumor tissue, Serum | GCR5 | Suppress progression | Therapeutic | [133] |
| miR-455 | ↑ | Tumor tissue | p27KIP1 | Oncogenesis | Prognostic | [132] |

Part VI: miRNAs involved in androgen receptor (AR) signaling

| miR-124 | ↓ | Tumor tissue | AR | – | – | – |
| miR-143/145 | ↓ | Tumor tissue | PROM1, CD44, OCT4, C- MYC, KLF4, ZEB2, AR | – | Diagnostic | [136] |
| miR-182 | ↑ | Tumor tissue | A5DRC3, FOX01 | Metastasis, Cell cycle | Therapeutic | [100] |
| miR-185 | ↑ | Tumor tissue | BRD8 IS02, 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-28a | ↓ | Tumor tissue | LIN28B, ZCCHC11 | – | Diagnostic | [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 | [96] |
| miR-126 | ↓ | Tumor tissue | ADAM9 | Proliferation | Diagnostic, Therapeutic | [122] |
| miR-130a | ↓ | Tumor tissue | DEPD1, SEC23B | – | – | – |
| miR-141 | ↑ | Tumor tissue, Serum, Exosomes | NR0B2, CD44, EZH2, Rho GTPases | Transcriptional activity in LNCaP cells, CSGs | Diagnostic | [90, 139] |
| miR-150 | ↓ | Tumor tissue | TRMP4 | Inhibition of PCa metastasis | Therapeutic | [106, 140] |
| miR-162 | ↑ | Tumor tissue | A5DRC3, FOX01 | AR signaling, Cell cycle | 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)
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 testosteronel 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-to-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 exosomes 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 embryonic 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 antimitic 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, miR-143 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, miRNA, [144], proteins, and enzymes. Exosomes act as a carrier in cellular communication. These membrane vesicles transfer their cargoes (DNA, mRNA, 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 recurrence 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 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
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 prognostic 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 (IncRNA) 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
IncRNAs, like PCAT18 and SCHLAP1, can be used as biomarkers for the identification of metastatic PCAs.

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 PCAs 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.

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