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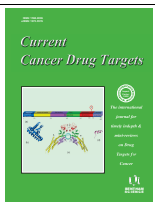
REVIEW ARTICLE

Role of MicroRNAs in Treatment Response in Prostate Cancer



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Abstract: Prostate cancer (PCa) is the most common non-skin cancer in men worldwide, resulting in significant mortality and morbidity. Depending on the grade and stage of the cancer, patients may be given radiation therapy, hormonal therapy, or chemotherapy. However, more than half of these patients develop resistance to treatment, leading to disease progression and metastases, often with lethal consequences. MicroRNAs (miRNAs) are short, non-coding RNAs, which regulate numerous physiological as well as pathological processes, including cancer. miRNAs mediate their regulatory effect predominately by binding to the 3′-untranslated region (UTR) of their target mRNAs. In this review, we will describe the mechanisms by which miRNAs mediate resistance to radiation and drug therapy (*i.e.* hormone therapy and chemotherapy) in PCa, including control of apoptosis, cell growth and proliferation, autophagy, epithelial-to-mesenchymal transition (EMT), invasion and metastasis, and cancer stem cells (CSCs). Furthermore, we will discuss the utility of circulating miRNAs isolated from different body fluids of prostate cancer patients as non-invasive biomarkers of cancer detection, disease progression, and therapy response. Finally, we will shortlist the candidate miRNAs, which may have a role in drug and radioresistance, that could potentially be used as predictive biomarkers of treatment response.

Keywords: MicroRNAs (miRNAs), biomarkers, prostate cancer, therapy response, radiation and drug therapy, apoptosis.

1. INTRODUCTION

Prostate cancer (PCa) is the most common non-skin malignancy affecting men, and the fifth leading cause of cancer related mortality in men [1]. Various treatment options are available, depending on the grade and stage of the tumour. The 5-year survival rate is excellent for patients with localised disease, but is considerably lower for advanced disease. Unfortunately, most patients develop resistance to drugs or radiotherapy, and this type of cancer is often aggressive, and has limited response to current treatment modalities [2, 3].

MicroRNAs (miRNAs) are non-coding ribonucleic acids (RNAs), 19-22 nucleotides long, which bind to the 3′- untranslated region (3′UTR) of their target mRNAs, leading either to mRNA destabilization or inhibition of translation [4-6]. miRNAs can also bind to the 5′UTR of target mRNAs, leading to enhanced translation [6]. Interestingly, each miRNA can target several hundred mRNAs, thus, playing a critical role in multiple physiological processes. Hence, their deregulation can lead to widespread detrimental effects. Studies have implicated various miRNAs in cancer initiation, progression and metastasis, by either acting as anti-neoplastic tumour suppressors (downregulated) or tumour promoting oncomiRs (upregulated), in a number of human malignancies, including PCa (reviewed in [7]). miRNAs have also garnered interest as potential biomarkers of cancer detection, progression, and treatment response [8]. Recently, the focus has shifted to circulating miRNAs, which can be isolated from various body fluids of cancer patients, in a non-invasive way. Advantages of circulating miRNAs as biomarkers include 1) their resistance to ribonuclease degradation and physiological conditions including high pH, incubation at room temperature for 24 hours, and frequent freeze-thawing, and 2) relatively easy quantification by PCR-based techniques [9].

In PCa, aberrant expression of miRNAs correlates with resistance to radiotherapy [10], hormone therapy [11], and chemotherapy [12]. This review will discuss the mechanisms by which miRNAs mediate treatment resistance. We have focussed on the miRNAs shortlisted here as they have been directly implicated in resistance to therapy, and their roles validated mostly by tissue specimen and/or *in vivo* studies (Table **1**). We have specifically tried to incorporate novel miRNAs, that have not been reviewed previously. In the second part of this review, we discuss circulating miRNAs, where we describe various body fluids that can be used to

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Table 1. miRNAs and their direct or functional known targets in prostate cancer. miRNAs can directly bind to the 3'UTR of their mRNA target to suppress its expression or indirectly by other unknown mechanisms.

miRNA	Role in	Expression Change	Direct or Functional Targets in Prostate Cancer	References
miR-212	CRPC	Downregulated	Lin28B SIRT1 hnRNPH1	[19] [22] [23]
miR-185	CRPC	Downregulated	AR BRD8 ISO2 SREBP-1,-2	[26] [27] [28]
miR-616	CRPC	Upregulated	TFPI-2	[29]
miR-221/222 cluster	CRPC	Upregulated*	p27(kip1) SIRT1 Caspase-10 HECTD2, RAB1A Ecm29	[39] [40] [41] [42] [43]
miR-146a	CRPC	Downregulated	ROCK1 Rac1	[46, 48] [49, 50]
miR-15a-16 cluster	Chemoresistance	Downregulated	CCND1, WNT3A CDK1, CDK2 CMYB, AR TGFβ & Hh pathway genes	[55] [56] [59] [60]
miR-200c	Chemoresistance	Downregulated	E-cadherin, EpCAM, Vimentin, ZEB1 TUBB-3, ZEB1, E-cadherin, Vimentin	[63-65] [65, 70]
miR-128	Chemoresistance	Downregulated	ZEB1 BMI-1	[72] [73]
miR-143	Chemoresistance	Downregulated	ERK5 HK2 KRAS FNDC3B	[75, 81] [76] [80] [82]
miR-31	Chemoresistance	Downregulated	E2F6 AR, E2F1, E2F2, EXO1, FOXM1, MCM2	[87, 91] [88]
miR-34a	Chemoresistance	Downregulated	CD44 LEF1 SIRT1, Bcl-2 BCL2 c-Myc BIRC5, TCF7	[92] [93] [94, 99] [95] [96] [97]
miR-521	Radioresistance	Downregulated	CSA	[103]
miR-95	Radioresistance	Upregulated	SGPP1	[106]
miR-106b	Radioresistance	Upregulated	Caspase-7	[111]
miR-320	CRPC, Chemoresistance	Downregulated	β-catenin LAMP1 AR	[116] [117] [118]
miR-21	CRPC, Chemoresistance	Upregulated	PTEN PDCD4 RECK $p57^{Kip2}$	[122] [125, 128] [129, 130] [131]
miR-32	CRPC, Radioresistance	Upregulated	BTG2 DAB2IP	[136] [138]
miR-205	CRPC, Chemoresistance, Radioresistance	Downregulated	BCL2L2 c-SRC BCL2 IL24, IL32 AR MED1 TP53INP1	[87] [140] [141] [142] [143] [145] [147, 148]

* indicates contradictory evidence of role in prostate cancer.

isolate and quantify miRNAs as potential biomarkers of drug- and radioresistance in PCa patients, concluding with the list of shortlisted potential candidates.

2. CASTRATION-RESISTANT PROSTATE CANCER (CRPC)

Prostate cancer cells need androgens for growth and proliferation, so disruption of androgen receptor (AR) signalling is a primary treatment option. Androgen receptor (AR) is a nuclear family transcription factor present in its inactivated form in the cytoplasm. AR dimerises upon ligand binding, and translocates to the nucleus, transcriptionally activating its target genes, leading to increased cell growth and proliferation [13, 14].

At diagnosis of metastatic disease, most PCa patients are androgen-sensitive, and therefore, androgen deprivation therapy (ADT) is the preferred treatment. ADT is also given as part of neo-adjuvant therapy, prior to primary therapy (radical prostatectomy or curative radiation therapy), to shrink the tumour mass, or as adjuvant systemic therapy for high-risk PCa patients, for whom metastatic disease is eventually a reality. Unfortunately, after initially responding to ADT, most patients develop resistance within 18-24 months, progressing to a more aggressive form of PCa, referred to as castration-resistant prostate cancer (CRPC). The progression of PCa from hormone-sensitive to hormone-resistant state is often accompanied by rising levels of serum prostate specific antigen (PSA) [15]. CPRC was previously designated as androgen-independent prostate cancer (AIPC) or hormone-refractory prostate cancer (HRPC) [11]. However, as ADT-resistant prostate cancers are still sensitive to AR pathway signalling, and respond to the nonsteroidal anti-androgenic drug abiraterone acetate [16], and AR antagonists like enzalutamide [17], the more accurate term is CRPC. In this review, we will use the term CRPC for patient studies, and androgen-independent (AI) and androgen-dependent (AD) when referring to PCa cell lines. There is currently no curative therapy available for CRPC patients [18].

2.1. Key miRNAs Implicated in CRPC

2.1.1. miRNA-212

miR-212 expression is downregulated in prostate tissue and serum samples from cancer patients compared with healthy controls [19]. Using an online tool, TargetScan, which predicts the mRNA targets of miRNAs, Lin28B mRNA was identified as a potential target of miR-212 [19]. This prediction was validated *in vitro*. Lin28B is an RNA binding protein, which plays an oncogenic role [20], and forms a regulatory loop with miR-212 *via* the c-Myc protein [21], resulting in increased growth in CRPC. miR-212 also regulates Sirtuin 1 (SIRT1) expression by binding to its 3′UTR, leading to inhibition of starvation induced autophagy, angiogenesis, and cellular senescence [22]. Recently, Yang *et al.,* investigated the causes of significantly higher incidence of PCa in African American men compared with Caucasian American men [23]. Decreased expression of miR-212 and aberrant expression of AR and the splicing regulator heterogenous nuclear ribonucleoprotein H1 (hnRNPH1) were associated with an increased incidence of PCa in African American men.

2.1.2. miRNA-185

miRNA-185 has been implicated many cancers including gastric [24], non-small cell lung cancer (NSCLC) [25], and PCa, where it is downregulated in comparison with non-cancerous cells [26]. miR-185 plays an important role in the transition of androgen-dependent PCa cells to androgen-independent cells by binding to the 3′UTR of AR mRNA and decreasing its expression [26]. Further, miR-185 also binds to the 3′UTR of the AR co-activator, bromodomain containing 8 isoform 2 (BRD8 ISO2), reducing its expression [27]. miR-185 along with miR-342 promotes caspase-dependent apoptosis in PCa cells by inhibiting the expression of an important transcription factor needed for lipogenesis, sterol regulatory element-binding protein-1 (SREBP1), and its downstream targets, fatty acid synthase (FASN) and 3-hydroxy 3-methylglutaryl CoA reductase (HMGCR), thereby impeding the tumorigenic potential of the cells [28]. Disruption of lipogenesis and cholesterogenesis halts tumour progression *via* inhibition of cell proliferation, migration and invasion *in vitro*, and regression of tumours *in vivo* (Fig. **1**).

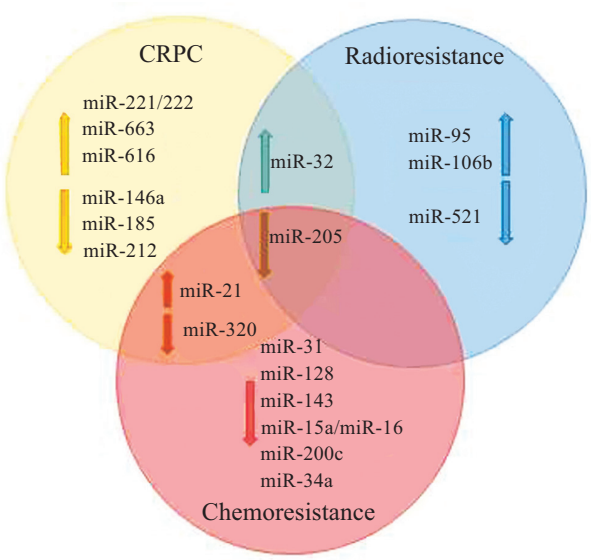

Fig. (1). miRNAs implicated in CRPC, chemo-, and radio-resistance. miRNAs may be upregulated or downregulated in all three types of resistances. A few miRNAs are common between CRPC and radio-resistance, CRPC and chemo-resistance, and in all three.

2.1.3. miRNA-616

miR-616 is overexpressed in PCa tissue compared to normal and benign prostate hyperplasia (BPH) tissue specimens, and also in androgen-independent (AI) PCa cell lines, but not in androgen-dependent (AD) or normal prostate epithelial cell lines [29]. LNCaP (AD) and 22rv1 (AI) cells are commonly used PCa cell lines. When miR-616 overexpressing LNCaP cells were injected into the nude mice, tumour growth remained unaffected even after bilateral orchiectomy, whereas tumour growth rate reduced for the control mice. 22rv1 cells with repressed miR-616 expression had delayed the tumour onset and cancer growth *in vivo*, suggesting that higher expression of miR-616 promotes castration-independent cell growth. miR-616 mediated the AI growth of

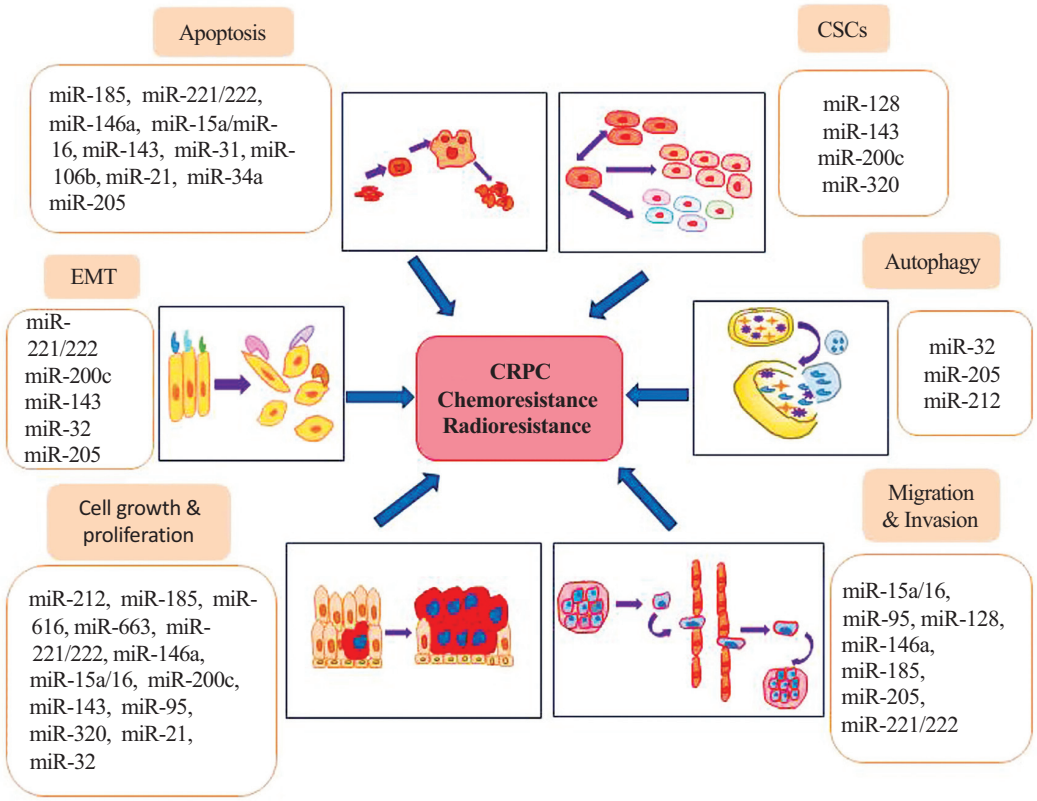

Fig. (2). Mechanisms by which miRNAs mediate their castration-resistant, chemoresistant, and radioresistant activities. These mechanisms include apoptosis, cell growth and proliferation, cancer stem cells (CSCs), autophagy, regulation of epithelial-to-mesenchymal transition, and cellular migration and invasion.

PCa cells by suppressing the expression of tissue factor pathway inhibitor-2 (TFPI-2), which acts as tumour suppressor in various cancers [30-32] including prostate cancer [33].

2.1.4. miRNA-663

There are conflicting results regarding the role of miR-663 in cancer. It appears to promote tumorigenesis and cell proliferation in nasopharyngeal carcinoma [34], but was reported to act as a tumour suppressor in pancreatic cancer [35], and glioblastoma [36]. In PCa, miR-663 expression level increases progressively from BPH to tumour tissue to CRPC tissue specimens, and AI cell lines [37]. This change in miR-663 expression correlated with poor clinical outcome and cancer recurrence in patients. Furthermore, overexpression of miR-663 promoted cell proliferation, invasion, and neuroendocrine differentiation in AI cells [37]. Increased expression of miR-663 may be due to binding of transcription factor Ets2 to its promoter. Ets2 activates the genes required for malignant transformation of PCa cells [38].

2.1.5. miRNA-221/222 Cluster

Overexpression of miR-221/222 has been associated with the prostate cancer cell progression from AD to AI. This may be mediated by miR-221/222 binding to the 3′UTR of p27/kip1, thereby decreasing p27/kip1 expression [39]. miRs-221/222 enhances cell proliferation [39, 40] and migration [40], but suppresses apoptosis [40, 41], and EMT [42] (Fig. **2**). However, not all studies confirm the oncogenic role of miRs-221/222 in PCa. Goto *et al.*, demonstrated that miR-221/222 expression was lost in PCa and CRPC tissues compared with the normal prostate epithelium [43]. Furthermore, loss of miR-221/222 expression *in vitro* was, in part, responsible for decreased invasive and migratory abilities of PCa cells, which appeared to be mediated by a scaffold protein Ecm29.

2.1.6. miRNA-146a

Tumour suppressor miR-146a inhibits cancer cell growth, migration and invasion [44, 45]. miR-146a expression is downregulated in AI versus AD PCa cells. In androgen-independent PC-3 cells, overexpression of miR-146a resulted in reduced cell proliferation, invasion, and adhesion. This occurred *via* suppression of the protein Rho-associated, coiled-coil containing protein kinase 1 (ROCK1) [46], which is a promoter of cancer cell invasion and anchorage-independent growth [47]. Another study confirmed this finding, by demonstrating that miR-146a mediates its caspase-3 dependent anti-apoptotic function in AI cells *via* binding to the 3′UTR of ROCK1 mRNA [48]. miR-146a also directly targets Rac1, a member of Rho family of small guanosine triphosphatases, leading to inhibition of apoptosis and augmentation of cell proliferation in AI cells [49, 50].

3. CHEMORESISTANCE

CRPC patients often develop metastases, particularly to the bones. Docetaxel is the preferred chemotherapeutic drug for such patients, although most develop resistance eventu-

ally [51, 52]. Currently, not many effective treatment options are available for docetaxel-resistant patients. Docetaxel acts by binding to microtubules leading to their stabilization, mitotic arrest, resulting in apoptosis [53]. Cabazitaxel, a new generation taxane, was approved recently for patients having docetaxel-resistance [54].

3.1. Key miRNAs Implicated in Chemoresistance

3.1.1. miRNAs-15a/miR-16

miRNAs miR-15a and miR-16 are candidate tumour suppressors, frequently downregulated in tissue specimens from PCa patients [55, 56]. Intriguingly, miR-16 expression (along with other miRNAs) is also decreased in normal prostatic tissue of PCa patients compared with tumour-negative healthy men (low-PSA) and tumour-negative controls (high-PSA), suggesting that this loss of expression occurs early during carcinogenesis [57]. The locus encoding miRNAs-15a and -16 is often homozygously deleted in PCa patients [58], and loss of miR-15a and miR-16 was associated with chemotherapy refractory behaviour of the PCa cells *in vitro* [55]. miR-15a and miR-16 were shown to promote apoptosis, impede cell proliferation, and reduce invasiveness of cancer cells by binding to the 3′UTRs of oncogenes CCND1 (encoding cyclin D1) and WNT3A (member of the wnt family of cysteine-rich, secretory glycoproteins) [55]. AntagomiRs are synthetic oligonucleotides used for knocking down specific miRNAs *in vivo*. Silencing of miR-15a and miR-16 in the prostates of Balb/c mice using antagomiRs augmented the invasive and proliferative potential of cancer cells. miR-16 overexpression also inhibited prostate tumour growth and bone metastasis in a PCa xenograft model, by decreasing the expression of cell cycle and apoptosis related genes, including Cyclin D3, CDK1, CDK2, Cks1, TAAC1, and TAAC3 [56]. Additionally, miR-15a impaired cell viability and migration by binding to the transcription factor cMYB and AR [59]. Loss of miR-15 and miR-16, along with the overexpression of miR-21 significantly increased the invasiveness of PCa cells, in addition to elevated likelihood of bone marrow metastasis [60]. Interestingly, levels of miR-15-miR-16 are not only decreased in prostate epithelial cells, but also in the surrounding cancer-associated fibroblasts (CAFs) [61].

3.1.2. miRNA-200c

miRNA-200c belongs to the miR-200 family, which includes miR-200a, miR-200b, and miR-429 clustered on chromosome 1, and miR-200c and miR-141 clustered on chromosome 12. miR-200 family members may control maintenance of epithelial characteristics, and their loss contributes to epithelial-to-mesenchymal transition (EMT) [62]. EMT is important in cancer metastasis and is associated with chemotherapy resistance. Commonly used epithelial markers are epithelial cell adhesion molecule (EpCAM) and E-cadherin, and mesenchymal markers are zinc-finger E-box-binding homeobox 1 (ZEB1), ZEB2, and vimentin. Expression of miR-200c is decreased in PCa cells [63, 64], and exogenous expression of miR-200c in DU145 cells resulted in reduced proliferative, migratory and invasive potential of the cancer cells *via* inhibition of EMT [65]. In PCa patients, neoadjuvant chemotherapy using docetaxel contributed to loss of E-cadherin and miRNAs -200c and -205, whereas, enforced expression of miR-200c and miR-205 *in vitro* sensitized cells to docetaxel treatment [63]. Interestingly, levels of EpCAM are decreased in docetaxel-resistant cells *in vitro*, which were restored when either or both miR-200c and miR-205 were made to express in the resistant cells [64]. Intriguingly, expression of miR-200 family members decreases when cells undergo EMT, and expression is restored during mesenchymal-to-epithelial transition (MET) [62]. Promoter hypermethylation, a mechanism by which genes are silenced [66], was shown to suppress miR-200c levels in PCa [67]. By analysing data from The Cancer Genome Atlas Data Portal, Gu *et al.*, suggested that a panel of tissue-derived miRNAs, including miR-200c, miR-182, and miR-221, could be used as a biomarker for PCa detection [68]. Cancer stem cells (CSCs) or tumour initiating cells may play a pivotal role in drug resistance by various mechanisms including enhanced DNA damage responses, ABC transporter expression, aldehyde dehydrogenase activity, and aberrations in key signal transduction pathways [69]. miR-200c along with miR-34a could modulate the hedgehog signalling pathway in CSCs in response to chemotherapeutic drug paclitaxel, resulting in CSC enrichment [70]. Paclitaxel alone could increase the CSC populations, but a combination of paclitaxel and hedgehog pathway inhibitor drug cyclopamine successfully countered this effect and induced apoptosis.

3.1.3. miRNA-128

Normal prostate cells express more miR-128 than invasive PCa cells [71, 72]. Induced expression of miR-128 in DU145 and LNCaP by miR-128 mimics sensitised cancer cells to the chemotherapeutic drug cisplatin [72]. ZEB1 was identified *in silico* and validated *in vitro* as miR-128 target. Decreased miR-128 expression resulted in higher ZEB1 expression, and maybe, responsible for increased invasiveness and chemo-refractory behaviour of PCa cells. A second study found that restoration of miR-128 expression correlated with reduced invasive potential of cancer cells *in vitro*, and suppressed tumour regeneration *in vivo* [73]. Tumour suppressive functions of miR-128 may also be mediated by binding to the proto-oncogene BMI-1, which is a regulator of prostate stem cells self-renewal and maintenance [74].

3.1.4. miR-143

miR-143 expression is progressively lost as the grade of PCa advances [75, 76]. Lower miR-143 correlated with enhanced cell growth, migratory and invasive ability of PCa cells *in vitro* and *in vivo* [77, 78]. KRAS is a member of well-known Ras family of GTP/GDP binding proteins, which promote AI cancer progression [79]. KRAS is suppressed by miR-143 in PCa cells, inactivating the downstream mitogen-activated protein kinase (MAPK) signalling pathway, and increasing docetaxel sensitivity [80]. The anti-proliferative and anti-migratory effects of miR-143 were a result of miR-143 binding to the 3′UTR of extracellular signal-regulated protein kinase 5 (ERK5) mRNA and limiting its expression [75]. The reverse correlation between miR-143 and ERK5 was confirmed by tissue microarray data from 168 PCa patients [81]. Further, miR-143 promoted apoptosis and G1/S cell cycle arrest, and decreased cell viability *via* binding to the 3′UTR of hexokinase 2 (HK2), an important enzyme for aerobic glycolysis [76]. However, not all studies

have substantiated miR-143 as tumour suppressor in PCa. Using spheres of PC-3 cells as a prostate cancer stem cell model, elevated expression of miR-143 was correlated with increased migration and invasion of CSCs [78]. Additionally, downregulated miR-143 suppressed metastasis in athymic nude mice. Functional studies revealed that fibronectin type III domain containing 3B (FNDC3B), an inducer of EMT, is a direct target of miR-143 [82].

3.1.5. miRNA-31

miR-31 is suppressed in various cancers, including nasopharyngeal [83], liver [84], oesophageal [85], and breast [86]. Normal prostate epithelial cells express high miR-31, whereas prostate tumours and PCa cell lines express low levels of miR-31 [87, 88]. Enforced expression of miR-31 and miR-205 rendered the cells sensitive to docetaxel and cisplatin [87]. Transcription factor E2F6, which inhibits hypoxia [89] and UV-induced apoptosis [90], is a direct target of miR-31. Inverse correlation between miR-31 and E2F6 was confirmed by another study [91], which established that a histone deacetylase inhibitor promoted apoptosis by activating miR-31 and consequently, inhibiting E2F6 expression. Intriguingly, AR and miR-31 mutually repressed each other, with AR binding to the promoter of miR-31 and miR-31 binding to the 3′UTR of AR mRNA, leading to the increased aggressiveness of the PCa cells [88]. Additionally, in tumours, miR-31 expression was suppressed by promoter hypermethylation.

3.1.6. miRNA-34a

Studies using cell lines, xenograft mouse models, and clinical specimens have established that miR-34a acts as a tumour suppressor in prostate cancer [92, 93]. miR-34a mediates its anti-tumourigenic actions by inhibiting cell proliferation [94, 95], inducing apoptosis [96, 97], inhibition of EMT, and suppressing migration and invasion *in vitro* [96], and impeding tumour growth and metastasis *in vivo* [98]. Restoration of miR-34a in PC3 cells inhibited cell growth and cell cycle progression, and induced apoptosis, indicating sensitization of cells to chemotherapeutic campothecin, along with growth inhibition and cell cycle arrest [99].

4. RADIORESISTANCE

Radiation based treatment or radiotherapy (RT) uses high energy rays or proton beams, which severely damage the DNA of cancer cells and induces apoptosis. Radiotherapy is given to patients as part of curative therapy, as an adjuvant therapy following radical prostatectomy [100], or as palliative therapy to relieve the bone pain, particularly in patients whose cancers have metastasised. Although the response rate to RT is about 60% for patients with localised tumours, up to 45% of patients develop recurrent PCa within 5 years [101, 102].

4.1. Key miRNAs Implicated in Radioresistance

4.1.1. miRNA-521

Josson *et al.,* performed miRNA screening on LNCaP and C4-2 cells four hours after radiation treatment, and found that expression levels of miR-521 decreased considerably [103]. Overexpression using miR-521 mimics sensitised the cells to RT, and miR-521 inhibition conferred resistance to RT. Mechanistic studies revealed cockayne syndrome protein A (CSA), a DNA repair protein, as a potential target of miR-521.

4.1.2. miRNA-95

Elevated levels of miR-95 have been linked to increased cell proliferation in colorectal cancer [104], and NSCLC [105], and are also associated with chemo- and radioresistance in NSCLC [105]. Next generation sequencing on parental radiosensitive and radioresistant PC3 cells generated by fractionated irradiation, identified miR-95 as increased in radioresistant cells [106]. Overexpression of miR-95 caused increased invasiveness, anchorage independent growth, and increased radioresistance of PC3 cells. In athymic nude mice, increased expression of miR-95 in PC3 cells correlated with quicker growth of the tumour. miR-95 targeted the 3'UTR of sphingosine-1-phosphate phosphatase 1 (SGPP1), as determined by reporter assay [106]. SGPP1 suppresses the invasive and migratory capabilities of cancer cells [107]. Interestingly, radioresistant PC3 cells also showed cross-resistance to commonly used chemotherapeutic drugs docetaxel and cisplatin.

4.1.3. miRNA-106b

miRNA-106b is an oncomiR in various cancers including hepatocellular carcinoma [108], cervical carcinoma [109], and colorectal cancer [110]. Recently, miR-106b overexpression in prostate tumours was linked with disease recurrence and metastasis, and shown to directly target caspase-7 [111]. Using a miRNA microarray on samples from LNCaP cells following irradiation, a number of miRNAs were found to be differentially expressed including miR-106b [112]. Increased expression of miR-106b by transient transfection with pre-miR-106b resulted in the suppression of cell cycle inhibitor p21 post radiation, causing G2/M arrest.

5. MIRNAS COMMON IN CRPC AND CHEMORESISTANCE

5.1. miRNA-320

miR-320 acts as a tumour suppressor in cancers, including osteosarcoma [113], glioma [114], and cervical cancer [115]. In PCa, miR-320 is lowly expressed in tumour tissues compared with normal prostate epithelium [116-118], and its overexpression resulted in reduced tumorigenic potential of PCa cells, both *in vitro* and *in vivo* [116]. Expression of miR-320 is further downregulated in tissue specimens from CRPC patients. miR-320 directly targeted lysosomal-associated membrane protein 1 (LAMP1) [117], which has been previously associated with tumour invasion and metastasis [119]. Knockdown of miR-320 in PCa cell lines increases the resistance to chemotherapy *via* enriching the $CD44^{high}$ CSC population [116]. Moreover, miR-320 mediates CSC inhibition by binding to 3′UTR of another target β-catenin. β-catenin is critical for self-renewal and maintenance of stem-like characteristics of the CSCs [120]. In PCa cell lines, histone deacetylase (HDAC) inhibitor OBP-801 reduced AR expression and tumour cell growth, by upregulating miR-320 expression [118]. miR-320 expression also

increased when PCa xenograft rats were treated with OBP-801, resulting in decreased tumourigenicity.

5.2. miRNA-21

OncomiR miR-21 has been implicated in numerous solid and haematological malignancies (reviewed in [121]). miR-21 is highly expressed in PCa tissues compared to normal prostate epithelia [122, 123]. Increased expression of miR-21 correlated with cancer recurrence in PCa patients following radical prostatectomy. Upregulated miR-21 correlated with more robust AD and AI growth of PCa cells *in vitro* and *in vivo* [124], and conferred resistance to docetaxel in PC-3 cells, conversely, miR-21 knockdown sensitized cells to docetaxel-induced apoptosis [125]. This oncogenic activity of miR-21 was mediated by binding to programmed cell death 4 (PDCD4), a tumour suppressor gene. PDCD4 is a direct target of miR-21 in breast [126], colorectal cancer [127], and PCa [128]. miR-21 promotes cell invasion *via* suppression of reversion-inducing cysteine-rich protein with Kazul motif (RECK), a matrix metalloproteinase inhibitor [129, 130]. Furthermore, by targeting the coding region of $p57^{Kip2}$, a cyclin-dependent kinase inhibitor, miR-21 promotes cancer cell migration and anchorage-independent growth in PC-3 and 22rv1 cells [131].

6. MIRNAS COMMON IN CRPC AND RADIORESISTANCE

6.1. miRNA-32

miR-32 was predicted to act as a tumour suppressor in multiple neoplasias, including NSCLC [132, 133], and gastric cancer [134]. In contrast, in colorectal cancer, miR-32 promoted cell growth, migration, and invasion by targeting PTEN [135]. miR-32 expression is regulated by androgen in PCa, and is increased in CRPC tissue specimens compared to PCa and benign hyperplasia samples [136]. LNCaP cells transfected with pre-miR-32 had reduced apoptosis compared to controls, and B-cell translocation gene 2 (BTG2) was identified as a target of miR-32 by mRNA microarray analysis [136]. Loss of BTG2 correlates with the oncogenic transformation of non-tumorigenic PCa cells [137], and a shorter progression free survival time in patients. miR-32 also binds to the 3′UTR to inhibit tumour suppressor DAB2IP [138]. Loss of DAB2IP induced EMT *in vitro* and promoted distant organ metastases in a xenograft mouse model [139]. Overexpressing miR-32 in PCa cell lines increased radioreistance, whereas its silencing sensitised the cells to radiation treatment. miR-32 appeared to mediate this effect *via* suppressing DAB2IP mediated autophagy [138].

7. miRNAs COMMON IN CRPC, CHEMORESISTANCE, AND RADIORESISTANCE

7.1. miRNA-205

miR-205 suppresses the growth of tumours in various malignancies, including PCa, where it targets c-SRC to limit growth [140], and Bcl2 and Bcl-w to promote apoptosis [87, 141]. miR-205 expression levels are significantly downregulated in PCa cells compared to normal cells [64, 142-144]. This downregulation can be due to hypermethylation of the miR-205 promoter [87, 145]. Interestingly, miR-205 is a target of tumour suppressor p63, which binds to the miR-205 promoter at two different sites [146]. Enhanced expression of miR-205 results in reduced cell migratory ability *via* inhibition of EMT. Recently, miR-205 was found play a part in irradiation-induced autophagy, possibly mediated by TP53INP1 [147, 148].

8. CIRCULATING MIRNAS AS NON-INVASIVE BIOMARKERS

The presence of circulating miRNAs in cancer patients was first demonstrated using the sera of Diffuse Large B-cell Lymphoma patients [149]. Building on this, Mitchell *et al.,* demonstrated the utility of circulating miRNAs as blood-based diagnostic tools using plasma and serum samples from PCa patients [9]. Since then, many body fluids have been used for the isolation of miRNAs to try and use differentially expressed miRNAs as diagnostic, prognostic, or predictive biomarkers (Table **2**). Recent research has suggested that circulating miRNAs may have a role in cell-to-cell communication as they are commonly found to be packaged in exosomes, microvesicles, and apoptotic bodies, and also associated with argonaute 2 protein [150-152].

Currently, serum PSA levels are used to monitor therapy response in PCa patients. This approach has shortcomings, for example, rising PSA is not always indicative of drug resistance or cancer recurrence. Some patients experience increased PSA levels when starting docetaxel treatment, even if they respond well, whereas, PSA levels may plunge in response to docetaxel in others. Interestingly, PSA levels do not show any increase even after local recurrence. There is a need for novel biomarkers that are better at predicting the treatment response. Here, we will briefly describe the potential biological sources and candidate miRNAs, which were expressed differentially between cancer *vs* non-cancer patients.

8.1. Plasma

Isolating tumour-derived miRNAs from plasma was first demonstrated using NOD/SCID mice, where expression of miR-629-3p and miR-600, could distinguish between the xenografted mice and controls [9]. Besides, they also measured the expression of six candidate miRNAs (miR-100, miR-125b, miR-141, miR-143, miR-205, and miR-296) in the sera of PCa patients and normal controls, and observed increased miR-141 levels in PCa patients. In another study, increased levels of miR-21 and miR-221 differentiated between localised PCa patients and healthy controls [153]. In the same study, while comparing patients with localised or advanced and metastatic disease, miR-141 emerged as the best indicator of cancer progression. The finding was corroborated by other studies [154, 155], and ability of miR-141 to predict cancer progression was equivalent to other biomarkers including serum PSA, circulating tumour cells (CTCs), and lactate dehydrogenase [154]. An Exiqon miRNA qPCR panel was used to profile 742 miRNAs in microvesicles from the plasma of localised (n=55), and metastatic patients (n=16), and healthy controls (n=28) [155]. Differentially expressed miRNAs included miR-141, miR-375, miR-107, and miR-574-3p. Additionally, microvesicle

Table 2. Circulating miRNAs used as biomarkers of prostate cancer detection, disease progression, and therapy response, isolated from various body fluids.

Source	Purpose	miRNA Candidates	References
Plasma	Diagnostic (PCa *vs* healthy)	miR-141	[9]
Plasma	Diagnostic (PCa *vs* healthy), Prognostic (local *vs* metastatic)	miR-21, miR-221, miR-141	[153]
Plasma	Predictive (treatment response)	miR-141	[154, 155]
Plasma Microvesicles	Diagnostic (PCa *vs* healthy), Prognostic (local *vs* metastatic)	miR-107, miR-574-3p, miR-141, miR-375	[155]
Plasma	Diagnostic (PCa *vs* BPH *vs* healthy)	miR-let-7c, miR-let-7e, miR-30c, miR-622, miR-1285	[156]
Plasma	Prognostic (low *vs* high-risk)	miR-20a, miR-21, miR-145, miR-221	[157]
Plasma	Prognostic (local *vs* mCRPC)	miR-16, miR-141, miR-151-3p	[158]
Plasma exosomal RNA	Predictive (drug response)	miR-1290, miR-375	[159]
Plasma	Predictive (drug response)	miR-20a, -20b, -21,-25,-132,-146a,-200a,-200b,-200c,-201b,-222,-375,-429,-590-5p	[160]
Serum	Diagnostic (PCa *vs* healthy)	miR-16, miR-34b, miR-92a, miR-92b, miR-103, miR-107, miR-197, miR-328, miR-485-3p, miR-486-5p, miR-574-3p, miR-636, miR-640, miR-766, mi-R885-5p	[161]
Serum	Diagnostic (PCa *vs* BPH *vs* healthy)	let-7i, miR-26a, miR-32, miR-195	[162]
Serum	Diagnostic (PCa *vs* healthy)	miR-24, miR-26b, miR-30c, miR-93, miR-106a, miR-223, miR-451, miR-874, miR-1207-5p, miR-1274a	[163]
Serum	Diagnostic (BPH *vs* PCa)	19 differentially expressed miRNAs	[164]
Serum	Prognostic (low *vs* high-grade)	miR-141, miR-200b, miR-375	[165]
Serum	Prognostic (local *vs* metastatic), Predictive (drug response)	miR-21	[166]
Serum	Prognostic (PCa *vs* mCRPC), Predictive (treatment response)	miR-141, miR-200a, miR-200c, miR-210, miR-375 miR-210	[167]
Serum	Prognostic (low-risk *vs* mCRPC)	miR-141, miR-375, miR-378a-5p, miR-409-3p	[168]
Serum	Predictive (biochemical recurrence)	miR-141, miR-146b-3p, miR-194	[170]
Serum	Prognostic (BPH or low-grade *vs* high-grade)	miR-let-7a, miR-24, miR-26b, miR-30c, miR-93, miR-100, miR-103, miR-106a, miR-107, miR-130b, miR-146a, miR-223, miR-451, miR-874	[171]
Urine	Diagnostic (PCa *vs* healthy)	miR-107, miR-574-3p	[155]

(Table 2) contd….

Source	Purpose	miRNA Candidates	References
Urine	Diagnostic (PCa *vs* healthy)	miR-205, miR-214	[172]
Urine	Diagnostic (PCa *vs* healthy)	miR-205, miR-183	[173]
Urine	Diagnostic (PCa *vs* BPH *vs* healthy)	miR-1825, miR-484	[174]
Urine	Diagnostic (PCa *vs* healthy)	miR-187	[175]
Urine	Diagnostic (PCa *vs* healthy)	miR-483-5p	[176]
Seminal Fluid	Diagnostic (PCa *vs* healthy), Prognostic (low *vs* high-grade)	miR-200b, miR-200c, miR-30a, miR-375, miR-99a miR-200b	[177]
Seminal Fluid	Diagnostic (PCa *vs* non-PCa)	miR-200c, miR-125b	[178]

and exosome derived miR-375 and miR-141 levels increased in patients with recurrent PCa after surgery compared to patients who did not relapse. To differentiate PCa (n=21) from BPH (n=17) patients, a screen of 754 miRNAs using Illumina Human v2 microarrays was performed [156], and identified candidates (miR-let-7c, miR-let-7e, miR-30c, miR-622, and miR-1285) were validated by qRT-PCR in a large cohort, including PCa (n=80), BPH (n=40), and healthy controls (n=54). Distinct expression patterns of miRNAs miR-20a, miR-21, miR-145, and miR-221 separated high-risk from low-risk patients [157]. miR-141, miR-151-3p, and miR-16 together could accurately distinguish between localised PCa and mCRPC with an improved sensitivity and specificity [158]. More recently, miR-375 and miR-1290 overexpression correlated with poor overall survival in CRPC patients [159]. miRNA profiling of CRPC patients before and after docetaxel chemotherapy yielded a number of differentially expressed miRNAs [160].

8.2. Serum

Besides plasma, serum is used for the isolation of miRNAs for the purpose of diagnosis [161-164] and predicting progression and [165], therapy response [166]. Elevated serum levels of miR-375, miR-141, and miR-200b distinguished between patients with low-grade (Gleason Score 6) and high-grade (Gleason Score 7) cancer, more efficiently than the currently used biomarker, PSA [165]. Increased miR-21 in the sera of CRPC patients, was particularly prominent for patients resistant to docetaxel [166]. To identify prognostic and predictive biomarkers, Cheng *et al.*, used TaqMan Low-Density Array to screen the miRNAs from the sera of mCRPC patients (n=25), and healthy controls (n=25) [167], and Nguyen *et al.,* carried out TaqMan miRNA array using the sera from mCRPC (n=26) and localised PCa patients (n=28) [168]. Both studies found increased expression of miR-375 and miR-141 in the serum samples of mCRPC patients, as well as other distinctly expressed miRNAs, including miR-200a, miR-200c, miR-210, miR-378a-5p, and miR-409-3p. miRNAs have also been used to predict treatment response in PCa, with increased expression of miR-141, miR-146b-3p, and miR-194 predictive of biochemical recurrence, which has been described as the PSA value of at least 0.4 ng/ml followed by another increase [169] in patients post radical prostatectomy [170]. To identify miRNAs that distinguish aggressive from indolent PCa, and predict biochemical recurrence, Mihelich *et al,* performed qRT-PCR analysis of 21 miRNAs from BPH, low- and high-grade PCa patients, and described a panel of 14 miRNAs that were considerably downregulated in high-grade PCa in comparison with BPH and low-grade PCa [171].

8.3. Urine

The expression of miRNAs in urine was measured in patients with and without PCa following a trans-rectal digital massage [155]. Expression of miRNAs miR-107 and miR-574-3p was increased in urine from PCa patients compared to controls. Another study found that downregulation of miR-205 and miR-214 levels could differentiate between healthy controls and PCa patients with 89% sensitivity and 80% specificity [172]. However, levels of miR-205 alone failed to differentiate PCa patients from the controls in a more recent study [173]. The role of urinary miRNAs in distinguishing PCa patients from benign prostate hyperplasia was investigated; two candidate miRNAs (miR-1825 and miR-484) correlated with the development and progression from benign prostate hyperplasia to PCa [174]. Interestingly, combining urinary miR-187 levels with other predictive factors including serum PSA and urinary prostate cancer antigen 3 (PCA3) was superior for predicting disease progression compared to PSA alone [175]. Recently the expression of three miRNAs (miR-483-5p, miR-1275, and miR-1290) was measured in freely voided urine samples [176]. Increased expression of miR-483-5p was observed in PCa patients but not in controls, suggesting that freely voided urine samples could be used for miRNA detection, bypassing the need for a digital rectal examination or prostate massage. However, miR-483-5p alone was not as robust as serum PSA in detecting PCa.

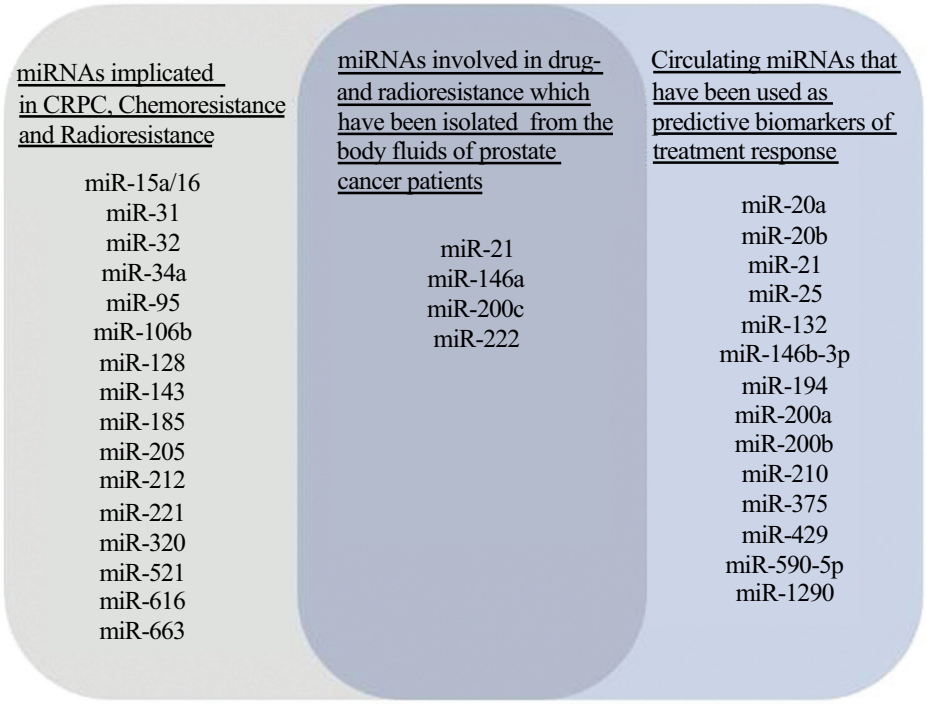

Fig. (3). miRNAs having a role in CRPC, chemoresistance, and radioresistance, which have evidence of being isolated from various body fluids of prostate cancer patients. Some miRNAs with good evidence for a role in drug- and radioresistance have also been isolated from the body fluids of cancer patients, and as such are good candidate biomarkers to predict patient responses to treatment.

8.4. Seminal Fluid

Recently, Selth *et al.,* looked into the possibility of using miRNAs isolated from the seminal fluid (SF) of prostate cancer patients for diagnostic and prognostic purposes [177]. A series of candidate miRNAs (miR-200b, miR-200c, miR-30a, miR-375, and miR-99a) were better diagnostic tools than serum PSA. Further analysis demonstrated that combining serum PSA with miR-200b levels was better at distinguishing PCa patients than the PSA alone. Additionally, miR-200b could also successfully separate low-risk patients (Gleason score 6) from high-risk patients (Gleason score > 7). The same group has also demonstrated that combining serum PSA with miR-200c and miR-125b expression, which were derived from the non-sperm cell fraction of the seminal fluid improves the specificity of PCa diagnosis compared to PSA levels alone [178].

CONCLUSION

In prostate cancer, accumulating evidence suggests that aberrant expression of miRNAs contributes to the development of castration-resistance, chemoresistance, and radioresistance in patients. Many studies have been performed *in vitro*, *in vivo*, or on human tissue samples to reach these conclusions.

Circulating miRNAs are promising candidates as non-invasive biomarkers that have been successfully isolated from plasma, serum, urine, and seminal fluid, with varying functional roles, be it as diagnostic, prognostic, or predictive biomarkers. Recently, strong candidates have emerged for use as diagnostic or prognostic markers, including miR-141, miR-21, miR-221, miR-375, miR-205. Others have been proposed as good predictive biomarkers of therapy response, including miR-141, miR-1290, miR-375, miR-200a, -b, and –c, miR-20a, and –b, miR-21, miR-25, miR-132, miR-146a, miR-201b, miR-222, miR-429, and miR-590-5p (from plasma), and miR-21, miR-210, miR-141, miR-146b-3p, and miR-194 (from serum). We have identified a panel of miRNAs that have also been successfully isolated from various body fluids, which play roles in drug- and radio-resistance, and could potentially be used as biomarkers of treatment response, including miR-21, miR-146a, miR-200c, and miR-222 (Fig. **3**). These miRNAs are promising candidates because their roles in drug- and radio-resistance have been validated by various tissue-based studies, and they are known to be isolated from body fluids of cancer patients undergoing therapy.

It is interesting to note that some of the miRNAs overlap between diagnostic, prognostic, and predictive categories, including the well-studied miR-141, miR-375, miR-21, and members of miR-200 family. Also worth mentioning is that we did not find any study which examined the potential of urine or seminal fluid miRNA(s) as biomarkers of treatment response. This would be an interesting topic for future research. A panel of miRNAs could be used in place of PSA, or as an adjunct to PSA, to improve its sensitivity and specificity.

Other key miRNAs that have been described here, for their role in drug- and radioresistance, but have not yet been isolated from the body fluids of cancer patients, should be evaluated for their potential as predictive biomarkers, and compared with the currently available and upcoming candidate biomarkers. Circulating miRNA research is still in its nascent stages, and more conclusive studies, with larger pa-

tient cohorts will be required to validate the use of circulating miRNAs as biomarkers of treatment response.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

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