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MicroRNAs and the Response of Prostate Cancer to Anti-Cancer Drugs

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Abstract: Despite considerable advances in early diagnosis, prostate cancer (PCa) remains the second leading cause of cancer-related deaths in men in western countries. In fact, although efficient therapies exist for early-stage disease, the treatment of advanced PCa remains unsuccessful mainly due to its poor responsiveness to anti-cancer agents. This evidence underlines the urgent need for the development of novel and more effective therapeutic approaches. In this context, the documented dysregulation of microRNAs (miRNAs) -which are short non-coding RNAs that regulate gene expression at post-transcriptional level- in PCa, together with their potential to simultaneously regulate multiple oncogenic/tumor-suppressive pathways, has stimulated interest in defining a functional association between altered expression of specific miRNAs and the response of PCa to anti-cancer agents. The purpose of this review is to provide an overview on PCa-related miRNAs as potential novel therapeutic targets/tools, with a special focus on the role that they may play in conditioning the responsiveness of PCa to anti-cancer drugs.

Keywords: Anti-cancer drugs, microRNA, prostate cancer.

1. AN OVERVIEW OF MicroRNAs

1.1. A Glimpse of microRNA Mechanism of Action

MicroRNAs (miRNAs) are a class of short non-coding RNAs (~22 nucleotides in length) that play a key role in modulating gene expression at post-transcriptional level, by causing either mRNA degradation or protein translation inhibition according to perfect or partial base pairing of their seed region and the target transcripts [1]. Since the discovery of the first miRNA in *Caenorhabditis elegans* [2], in the last two decades hundreds of miRNAs have been identified in almost all multicellular organisms, including plants, worms, flies, fish and mammals [3-6], as well as in DNA viruses [7]. To date, more than 14,00 miRNAs have been discovered in humans (annotated in miRBase database, www.mirbase.org), where they represent one of the most abundant classes of regulatory genes and are involved in the control of almost all critical biological and physiological processes, including development, proliferation, differentiation, adhesion, angiogenesis and apoptosis [8].

miRNAs biogenesis (Fig. **1**) is a multi-step process that involves several key regulator factors and begins in the nucleus with the transcription of miRNA genes, which, in mammalian cells, are located within the introns of protein-coding genes, within exons/introns of long non-coding RNAs or may be present as independent transcriptional units [9]. In the first step of the biogenesis, miRNA genes are transcribed by the RNA polymerase II into 100-1000 bp-long primary transcripts (pri-miRNAs), that are characterized by a double-stranded stem-loop structure and contain a 7-methylguanosine cap at the 5' end and a polyadenylated tail at the 3' terminus [9]. Still in the nucleus, the pri-miRNA is processed into a ~70-nucleotides long precursor (pre-miRNA) by the RNase III enzyme Drosha in association with its co-factor DGCR8 (DiGeorge syndrome critical region gene 8). Subsequently, the pre-miRNA is exported *via* the RanGTP nuclear receptor XPO5 (Exportin-5) into the cytoplasm where it is processed into a 21-24 nucleotide-long miRNA duplex (miRNA:miRNA*) by the RNase III enzyme Dicer. During the miRNA maturation process, the strand of the miRNA duplex that will become the mature, active miRNA is selected according to the thermodynamic stability of the duplex itself, which will be unwound from the more energetically favorite terminus. Once correctly selected, the mature miRNA is incorporated into a multi-component complex known as miRISC (miRNA-RNA inducing silencing complex), composed of Argonaute protein (AGO) family members and ancillary factors that mediate miRNA/mRNA recognition and subsequent target regulation [8, 10].

miRNA target sequences are mainly located in the 3'-UTR (untranslated region) of target mRNA, although they can be also found in the 5'-UTR or in the open reading frame [11]. As previously mentioned, depending on the degree of complementarity with its target mRNA, a miRNA can negatively regulate gene expression either by mRNA degradation or inhibition of the translation. However, to further complicate the intricate role exerted by miRNAs in the regulation of gene expression, recent evidence suggests that miRNAs may also target specific sequences in gene promoters, thus favoring gene transcription, a phenomenon known as RNA activation (RNAa) [11, 12]. In this context, Vasudevan and col-

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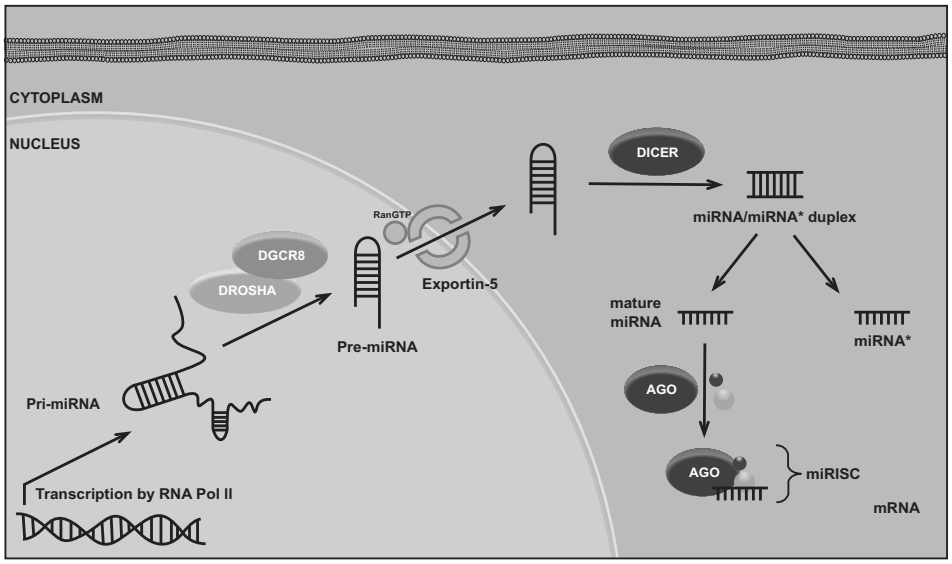

Fig. (1). Schematic representation of miRNA biogenesis and maturation. The key steps bringing to the final mature form of a miRNA are shown.

leagues [13] first reported that let-7 can switch repression to activation of translation according to cell proliferating status.

1.2. miRNAs in Cancer

Alterations of physiological miRNA expression levels can lead to a number of human diseases, including cancer [9]. The first evidence of a direct involvement of miRNAs in human cancer was reported in 2002 by Calin and colleagues during the characterization of the 13q14.3 deletion, the most frequent chromosomal anomaly associated to human B-cell chronic lymphocytic leukemia (CLL) [14]. The vain attempt to identify a protein-coding gene causal for leukemia predisposition and residing in the deleted 30-Kb region led the researchers discover two miRNA genes, namely, miR-15a and miR-16-1, located within the locus. Accordingly, both miRNAs are absent or down-regulated in most CLL patients [14]. Successively, Cimmino *et al.* [15] demonstrated that the anti-apoptotic protein Bcl-2 is a direct target of miR-15a and miR-16-1, thus suggesting that the loss or down-modulation of such miRNAs may contribute to malignant transformation by up-regulating Bcl-2.

Since then, hundreds of miRNAs have been reported to play a key role in tumor initiation and progression [8]. The development of different high-throughput technologies has indeed permitted to analyze the miRNA global expression profiles in pathological *vs* normal tissues [16]. In this context, growing evidence indicates that tumor tissues show typical miRNA signatures (*i.e.,* miRNome, miRNA fingerprints) -made of both up- and down-regulated miRNAs- that have been proven to be a useful tool to discriminate between normal and tumor tissues and to identify different cancer subtypes [17]. In addition, in the context of specific cells/tissues, the analysis of the miRNome has allowed to identify miRNAs as markers of prognosis and as indicators of treatment response [17]. The aberrant miRNA expression levels in tumors *vs* normal counterparts can be dependent on several mechanisms, including gene deletions, amplifications, point mutations, dysregulations (gain or loss) of transcription factors, changes in epigenetic regulatory mechanisms (such as DNA methylation and histone modifications), as well as perturbations in the machinery responsible for miRNA biogenesis and maturation [18].

Deregulated miRNAs in tumors trigger a global perturbation in the expression and/or function of their downstream targets. In fact, a single miRNA can target many different mRNAs and a single mRNA can be targeted by several miRNAs. However, since the expression patterns of miRNAs and their respective targets may differ among tissues and differentiation states, miRNAs may act as tumor suppressors or oncogenes (oncomir) depending on the cell/tissue context and the presence of relevant targets [19]. Moreover, given that cancer-associated miRNAs often affect factors involved in the response of cells to anti-cancer drugs or radiation (such as drug resistance-associated proteins, apoptosis-associated and DNA repair factors), miRNAs have been suggested as key determinants of chemo- and radio-resistance [17].

2. ROLE OF miRNAs IN THE RESPONSE OF PROSTATE CANCER TO ANTI-CANCER DRUGS

Prostate cancer (PCa) is the most prevalent tumor in the male population and the second leading cause of cancer-related death in man in western countries [20]. Organ-confined disease is successfully treated with radical prostatectomy or radiotherapy [21]. Androgen deprivation therapy is currently used to treat patients with metastatic PCa [22]. However, the efficacy of such a therapeutic option is time-limited and most patients develop a castration-resistant disease [22]. Castration-resistant PCa continues to rely on the androgen receptor for growth and progression, as recently demonstrated by the impact exerted on patient overall survival by two drugs, abiraterone acetate and enzalutamide, that ultimately function by decreasing the androgen receptor signaling [23]. The acquisition of the castration-resistant

phenotype represents one of the key events in the progression of PCa, which, at this stage, becomes also refractory to chemotherapeutic agents, although taxanes, such as docetaxel and, more recently, cabazitaxel, have demonstrated overall survival benefit [23].

Anti-cancer drug resistance is a multifactorial phenomenon involving several major mechanisms. In recent years, a considerable effort has been made to characterize specific alterations associated to the poor responsiveness of PCa to anti-cancer agents, with the aim to identify new targets to be used for the development of innovative therapies [24]. In this context, a few published studies have been focused on the identification of deregulated miRNAs and the evaluation of the consequences of their modulation with the dual aim to produce a direct anti-cancer effect and to increase PCa sensitivity to anti-cancer agents.

A variety of experimental approaches have been used to artificially modulate miRNA expression in PCa models. Specifically, the inhibition of the expression of up-regulated oncogenic miRNAs has been accomplished through the use of "antisense" oligonucleotides carrying chemical modifications to increase stability and resistance to nucleases. The most widely used "antisense" oligonucleotides are antagomirs -which contain a phosphorothioate linkage and are conjugated with a cholesterol mojety- and locked nucleic acids (LNAs) [25, 26]. To transiently restore the expression of down-regulated miRNAs, miRNA mimics (small, chemically modified double-stranded RNAs that mimic endogenous miRNAs) are largely used. An alternative approach to stably over-express down-regulated miRNAs is accomplished by cloning miRNA genes into plasmid or viral vectors [25, 26].

2.1. miRNAs as Determinants of Resistance to Anti-Cancer Drugs and Targets for Treatment Response Modulation

Studies carried out in *in vitro* and *in vivo* models led to the identification of a small panel of miRNAs whose experimental modulation was able to modify the responsiveness of PCa to a variety of anti-cancer drugs (Table **1**).

miR-21. miR-21 -which is located on chromosome 17- is one of the most studied miRNAs thus far [27]. Although still debatable [19], miR-21 has been found widely over-expressed in multiple cancers and is thought to play a pivotal role in tumorigenesis [28-36]. Specifically, it has been demonstrated to counteract the expression of a plethora of target proteins [37-39], thus resulting a key player in the regulation of basic hallmarks of cancer. Several preclinical studies have demonstrated that inhibition of miR-21 affects tumor cell growth and survival, invasion and migration as well as the response of cancer cells to conventional anti-cancer therapies. Altogether, these observations have contributed to identify miR-21 as an oncomiR and as a suitable therapeutic target for anti-cancer interventions [17].

To date, scanty and contradictory information is available concerning the role of miR-21 in PCa. In fact, it was initially described as one of the six miRNAs the over-expression of which may represent the signature for solid tumors, including PCa [40]. Successively, Ribas *et al.* [41] found that miR-21 levels are frequently elevated in early grade PCa samples in comparison to adjacent normal tissue. They also demonstrated that miR-21 over-expression stimulates the growth of both castration-sensitive and -resistant PCa cell lines, enhances tumor xenograft growth and promotes androgen-independent proliferation following surgical castration [41, 42], thus supporting an oncogenic role for miR-21. By contrast, Hulf *et al.* [43], using an integrative approach that combines primary transcription and genome-wide DNA methylation with miRNA expression, found miR-21 to be epigenetically repressed in PCa cells, thus suggesting that it may instead act as a tumor suppressor gene. We found miR-21 expression levels to be similar in tumor and matched non-neoplastic tissues from PCa patients who underwent radical prostatectomy and failed to appreciate differences in the miRNA expression levels as a function of nodal status, extraprostatic extension of the disease and Gleason score [19]. In addition, in our hands LNA-mediated miR-21 knockdown did not affect the proliferative and invasive capabilities, as well as the responsiveness to anti-cancer drugs (cisplatin and paclitaxel) and ionizing radiation of castration-resistant PCa cell lines [19]. Conversely, Shi and colleagues [44] recently found a relationship between miR-21 expression levels and the responsiveness of PCa cells to docetaxel, showing that miR-21 ectopic reconstitution or deletion resulted in increased resistance or sensitivity, respectively, to the taxane.

Based on aforementioned information, a consensus on miR-21 as a modulator of PCa to specific anti-cancer drugs has not yet been achieved, owing to large incongruities in the experimental data collected so far.

miR-34a. The three members of miR-34 family are produced from two transcriptional units: miR-34a is transcribed from chromosome 1, whereas miR-34b and miR-34c share a common primary transcript obtained from a region on chromosome 11 [45]. Often deregulated (lost or reduced) in tumors [46-50] -wherein its expression has been shown to be dependent on the tumor suppressor p53 [45]-, miR-34a has been demonstrated to control the expression of several target proteins involved in cell proliferation, cell cycle progression, apoptosis, invasion and migration [45].

Results from miRNA profiling analysis indicated that miR-34a expression levels are reduced in PCa compared to normal prostate tissues [51, 52]. miR-34a expression levels are also higher in p53 wild-type (LnCAP) than in p53-null (PC3) or p53-mutated (DU145) PCa cells [53], suggesting that reduced miR-34a expression levels in PCa could be ascribable, at least in part, to p53 defects. Such a hypothesis was corroborated by the evidence that ectopic expression of p53 in p53-defective PC3 cells increased miR-34a expression [53]. Transfection of p53-null PCa cells with miR-34a synthetic precursor caused cell growth inhibition and the concomitant appearance of cells with a senescence-like phenotype [53].

miR-34a expression is down-regulated in CD44+ cells -which are characterized by enhanced clonogenic, tumor-initiating and metastatic capacities- purified from PCa xenografts and primary tumors. Enforced expression of miR-34a decreased clonogenic expansion and tumor regeneration in both bulk and purified CD44+ PCa cells [54]. Moreover, systemically delivered miR-34a reduced lung metastasis and

Table 1. Summary of MiRNAs whose modulation modifies the responsiveness of PCa cells to specific anti-cancer drugs.

miRNA	Expression*/Role in PCa	Cell Model	Approach Used for miRNA Modulation	Effect on the Sensitivity to Anti-Cancer Drugs	Ref.
miR-21	=	DU145 PC3	Transfection with LNAs	Cisplatin, paclitaxel (=)	[19]
	↑ / Oncogene	Docetaxel-resistant PC3	Transfection with antisense oligonucleotides	Docetaxel (↑)	[44]
miR-34a	↓ / Tumor Suppressor	Docetaxel-resistant PC3 and 22Rv1	Transient transfection with miRNA mimics	Docetaxel (↑)	[55]
		Paclitaxel-resistant PC3		Paclitaxel, Daunorubicin, Etoposide (↑)	[56]
		Parental PC3		Camptothecin (↑)	[53]
miR-125b	↑ / Oncogene	LnCAP-cds PC-346C	Transfection with antisense oligonucleotides	Cisplatin (↑)	[72]
miR-143	↓ / Tumor Suppressor	DU145 PC3	Transient transfection with miRNA mimics	Docetaxel (↑)	[84]
miR148a	↓ / Tumor Suppressor	Parental PC3 Paclitaxel-resistant PC3	Transient transfection with miRNA mimics	Paclitaxel (↑)	[87]
miR-200b	↓ / Tumor Suppressor	DU145 PC3	Transient transfection with miRNA mimics	Docetaxel (↑)	[92]
miR-205	↓ / Tumor Suppressor	DU145 PC3	Transient transfection with miRNA mimics	Cisplatin, doxorubicin (↑)	[101]
		WPE1-NA22 WPE1-NB26	Stably-transfected clones with a precursor sequence cloned into a viral vector	Cisplatin, docetaxel (↑)	[104]
		DU145	Stably-transfected clones with a plasmid	Cisplatin (↑)	[112]

*,expression in PCa *vs* normal cells/tissues (=, unchanged expression levels; ↑, up-modulated; ↓, down-modulated)
(↑), increased responsiveness to anti-cancer drugs
(=), unmodified responsiveness to anti-cancer drugs

prolonged survival of human PCa-bearing mice as a consequence of the down-regulation of CD44, a direct target of the miRNA [54].

In the attempt to identify potential clinically relevant biomarkers of docetaxel-resistance, Corcoran and colleagues [55] performed a global profiling of intracellular and extracellular (cell-derived exosomes) miRNAs in castration-resistant PCa cell lines with acquired resistance to docetaxel (PC3RD, DU145RD and 22Rv1RD) and their parental cell lines (PC3, DU145 and 22R1v). Such an analysis revealed that four miRNAs (miR-598, miR-34a, miR-146a, miR-148a) are significantly decreased in cells and exosomes of two of the three docetaxel-resistant variants [55]. Functional studies showed that mimicked expression of miR-34a in docetaxel-resistant PC3RD and 22Rv1RD cell lines caused a significant increased in the anti-proliferative effect of docetaxel [55]. Similarly, the ectopic expression of miR-34a attenuated the resistance of established paclitaxel-resistant PC3 (PC3PR) cells and concomitantly increased their sensitivity to drugs with different mechanism of action, such as daunorubicin and etoposide [56]. In addition, transfection of parental PC3 cells with the miR-34a precursor significantly enhanced their sensitivity to camptothecin as a consequence of an enhanced apoptotic response [53]. The described chemo-sensitizing effects are ascribable, at least in part, to the miR-34a-dependent suppression of SIRT1 and Bcl-2 [53, 55, 56]. Altogether, these data support miR-34a reconstitution as a promising strategy to counteract the drug-resistant phenotype of castration-resistant PCa cells, irrespectively of p53 status.

A different scenario would appear to arise for castration-sensitive PCa. In fact, Rokhlin and colleagues [57] showed that inhibition (or forced expression) of either miR-34a or miR-34c was not able to modulate doxorubicin-mediated apoptosis in p53 wild-type LNCaP cells. However, simultaneous over-expression of both miRNAs in the same experi-

mental model resulted in improved p53-mediated apoptotic response following doxorubicin treatment, whereas their concomitant inhibition resulted in the suppression of doxorubicin-mediated apoptosis [57]. Although based on a single cell model, these findings suggest that modulation of miR-34a alone is not sufficient to produce a chemosensitizing effect, and corroborate the notion that the role exerted by a specific miRNA is highly dependent on the specific cellular context.

miR-125b. miR-125b belongs to the miR-125 family which is composed of three homologs: miR-125a, miR-125b-1 and miR-125b-2 [58]. MiR-125a is located at 19q13, while miR-125b is transcribed from two loci located on chromosomes 11q23 (miR-125b-1) and 21q21 (miR-125b-2) [59]. All members of the family play crucial roles in a variety of cellular processes, including cell differentiation, proliferation and apoptosis [59]. Aberrant expression of miR-125b has been reported to occur in several solid [60-64] and hematologic [65-67] malignancies, where it has been found to act alternatively as an oncogene or a tumor suppressor depending on the tumor type [59].

As far as PCa is concerned, although an early investigation reported that miR-125b was down-regulated in 5 of 9 tumors compared to 4 benign prostate samples [68], several subsequent studies demonstrated that miR-125b is over-expressed in PCa clinical samples and cell lines compared to normal prostate tissues [69-71]. The enforced expression of miR-125b also stimulates the androgen-independent PCa growth both *in vitro* and *in vivo*, where it promotes tumor growth in both intact and castrated male nude mice [59, 69]. Based on such evidence, in PCa miR-125b is viewed as an oncogene. Indeed, miR-125b inhibits the intrinsic apoptotic pathway and promotes the proliferation of PCa cells through the regulation of p53, PUMA, Bak1 and $p14^{ARF}$ [69, 72, 73]. Moreover, miR-125b knock-down in castration-sensitive PCa cells reduces cell proliferation and sensitizes LNCaP-cds (generated by chronic androgen withdrawal) and PC-346C (established from a transurethral resection of a primary tumor) cells to GCP (an isoflavone-enriched fermentation product with anti-PCa activity both *in vitro* and *in vivo* [74]) and cisplatin, respectively, by inducing an enhanced apoptotic response [72]. Altogether, these data suggested that, through the impairment of the apoptotic machinery, miR-125b concurs, at least in part, to the drug-resistant phenotype of PCa cells.

miR-143. miR-143 is a highly conserved miRNA that clusters with miR-145 on chromosome 5. Both miRNAs have been shown to be down-regulated in multiple human malignancies [75-80] and have been extensively studied as potential tumor suppressors since they are involved in the regulation of several cancer-relevant events such as proliferation, migration and invasion [80].

The expression levels of miR-143 have also been reported to be significantly down-regulated during PCa development and progression [81, 82]. A recent study showed that loss of miR-143 expression in PCa correlates with up-regulation of ERK5, favoring cell proliferation, survival, and invasion, and leading to the development of more aggressive forms of PCa [83]. Transfection of castration-resistant PCa cells with miR-143 mimic abrogated cell growth both *in vitro* and *in vivo* [81, 83, 84] and inhibited migration [84]. Notably, over-expression of miR-143 enhanced the responsiveness of DU145 and PC3 cell lines to docetaxel by targeting EGFR/RAS/MAPK pathway [84], thus supporting the reconstitution of miR-143 as an attractive therapeutic strategy to inhibit PCa growth and modulate its responsiveness to taxanes.

miR-148a. Members of the miRNA-148/152 family (miR-148a, miR-148b, and miR-152), are implicated in the pathogenesis of several diseases, including cancer [85]. Growing evidence indicated that the expression levels of miR-148/152 family members significantly decreased in tumors compared to normal tissues, thus suggesting that they may act as tumor suppressors [85]. The functional role of miR-148/152 family members in PCa is largely unknown. However, miR-148a expression has been reported to be lower in aggressive PCa (Gleason score 8) than in normal adjacent tissues, as well as in castration-resistant PCa than in benign prostatic hyperplasia [68, 86]. In addition, Fujita *et al.* [87] demonstrated that the levels of miR-148a were significantly reduced in castration-resistant PCa cells with respect to both normal prostate epithelial cells and castration-sensitive PCa cells. Transfection of castration-resistant PCa cells with miR-148 precursor induced inhibition of cell growth, migration and invasion, indicating that dysregulation of miR-148a expression could contribute to the metastatic potential of PCa cells [87]. In addition, ectopic expression of miR-148a sensitized PC3 cells and attenuated the resistance of paclitaxel-resistant PC3 cells to paclitaxel by regulating MSK1 expression [87].

miR-200 family. The miRNA-200 family consists of five members (*i.e.,* miR-200a, miR-200b, miR-200c, miR-429, and miR-141) which can be divided into two clusters: the miR-200ab/429 cluster containing miR-200a, miR-200b, and miR-429 (located on chromosome 1), and the miR-200c/141 cluster, which contains miR-200c and miR-141 (located on chromosome 12) [88]. The role of miR-200 family members as tumor-suppressors has been extensively demonstrated in several human malignancies [88]. However, there are only few reports linking miR-200 family members with PCa, wherein they have been recognized to be down-regulated along tumor progression and to play a critical role in the suppression of epithelial-to-mesenchymal transition (EMT), tumor cell invasion and metastasis [89-92]. Accordingly, over-expression of miR-200b in castration-resistant PCa cells significantly inhibited their proliferation and reduced the formation of tumors s.c. upon xenotransplantation into nude mice [93]. Moreover, in an orthotopic model, miR-200b reconstitution was found to counteract spontaneous metastasis [93]. Such an effect was mainly due to the reversion of EMT [93]. Ectopic expression of miR-200b in castration-resistant PCa also suppressed cell proliferation and migration [92].

Puhr and colleagues [94] first reported a relationship between the docetaxel-resistant phenotype and the appearance of EMT in castration-resistant PCa sublines (DU145-DR and PC3-DR), with experimentally induced resistance to taxane. Specifically, performing a screening for key regulators of an epithelial phenotype, the authors found a significantly reduced expression of miR-200c (and miR-205) in docetaxel-

resistant compared to parental cells. Transfection of resistant cells with both miRNAs resulted in re-expression of E-cadherin and down-regulation of ZEB1 and ZEB2, accompanied by increased apoptosis, thus suggesting that reduced miR-200c (and miR-205) levels during chemotherapy are crucial for cancer cell survival and drug resistance [94]. Unfortunately, the authors did not address the impact of miRNA restoration on the sensitivity profile of PCa cells to docetaxel. However, Yu *et al.* [92] reported that transfection of DU145 and PC3 cells with another member of the miR-200 family, miR-200b, improved their sensitivity to docetaxel by regulating Bmi-1. Although a possible correlation between the expression levels of miR-200-family members and responsiveness of PCa cells to docetaxel is envisaged, further investigation is warranted.

miR-205. To date, there is much but controversial information regarding the role of miR-205 in cancer. In fact, it was found to be either up- or down-regulated in tumors compared with normal tissues [95-98]. With regard to PCa, miR-205 has been extensively reported to be down-regulated in PCa compared to adjacent non-neoplastic tissue [99-104], as well as in PCa cell lines, irrespective of their androgen responsiveness, compared with normal cells [99, 103-105]. Recent studies have also shown that miR-205 expression is inversely correlated with total/free PSA levels and tumor stage [104, 105-108]. Moreover, miR-205 levels were found to be significantly decreased in primary tumors from patients with lymph node dissemination compared to those from node-negative patients [99]. In addition, miR-205 expression is down-regulated in lymph node metastasis compared to the primary tumor [103], suggesting that miR-205 is critically involved in distinct processes leading to migration, invasion and/or homing of metastatic PCa cells.

We previously reported that miR-205 acts as a tumor suppressor in human PCa, as its restoration in castration-resistant PCa cells resulted in cell rearrangements consistent with a mesenchymal-to-epithelial transition (*i.e.,* up-regulation of E-cadherin, reduction of cell locomotion/invasion, increased sensitivity to anoikis) [99]. Over-expression of miR-205 was also shown to cause cell proliferation decline, cell cycle perturbation and apoptosis induction in both castration-sensitive and -resistant PCa cells, by inhibiting specific targets such as Bcl-2, Bcl-w and c-SRC [102, 103, 105]. In addition, we demonstrated that miR-205 reconstitution triggers the reactivation of basement membrane deposition thus allowing a 3D organization of PCa cells into normal-like acinar structures [109] and interrupts the pro-invasive circuitries engaged by reactive stroma [110].

Since EMT is known to play an important role in treatment resistance [111, 112] and miR-205 is able to counteract EMT in PCa, it has been hypothesized that its restoration could represent a new therapeutic approach to sensitize PCa to drugs with different mechanism of action. Accordingly, Verdoot *et al.* [102] and Bhatnagar *et al.* [105] reported that over-expression of miR-205 sensitized PCa cells to cisplatin, docetaxel and doxorubicin by enhancing the apoptotic response as a consequence of the inhibition of anti-apoptotic members of the BH3 family (*i.e.,* Bcl-2 and Bcl-w). In this context, we recently demonstrated that the enhancement of cisplatin cytotoxic activity in castration-resistant PCa cells following miR-205 reconstitution is only partially dependent on apoptosis induction and mainly relies on miRNA-dependent impairment of the autophagic flux [113], thus suggesting a tight interconnection between the mesenchymal phenotype and autophagy, an evolutionarily conserved mechanism that traffics materials from cytoplasm to lysosomes *via* autophagosomes [114]. Specifically, miR-205 reconstitution led to a marked down-regulation, among others, of *LAMP3* and *RAB27A* genes, that are specifically associated with lysosome function and trafficking, thus resulting in a constraint on the autophagic flux [113]. Altogether these findings indicate miR-205 reconstitution as a promising approach to improve the response of PCa to anti-cancer drugs.

2.2. Clinical Relevance of miRNAs as Predictive Biomarkers of Treatment Response

Due to their presence and stability in body fluids (such as blood and urine), miRNAs represent perhaps the best opportunity for developing novel non-invasive approaches for predicting and monitoring tumor response to treatment [115]. Thus far, the possible relevance of circulating miRNAs as biomarkers of response to chemotherapy in PCa has been investigated in two studies. In the first one, Zhang *et al.* [116] evaluated the expression levels of miR-21 in serum samples from 10 hormone-refractory PCa patients who underwent docetaxel-containing treatment. Study results indicated that miRNA-21 levels were significantly higher in patients who were resistant to docetaxel-based chemotherapy when compared to those sensitive to treatment.

More recently, Li *et al.* [117] performed a global miRNA profiling in docetaxel-sensitive and-resistant cell lines to identify candidate miRNAs and then evaluated the expression levels of the best 46 candidate miRNAs in plasma/serum samples collected before and after docetaxel treatment from 97 castration-resistant patients. Non responders to docetaxel and patients with shorter survival showed high pre-treatment levels of miR-200 family members or decrease/unchanged post-treatment levels of miR-17 family members. In addition, in multivariable analysis, pre-treatment miR-200b levels were found to be an independent predictor of overall survival.

Although these studies results have envisaged the possibility of establishing a correlation between the expression of specific miRNAs and docetaxel chemotherapy outcome, further investigation in clinical trials is warranted.

CONCLUDING REMARKS

Results obtained in PCa experimental models through the use of different miRNA-modulating approaches have provided evidence of a direct involvement of specific miRNAs in the responsiveness of PCa to anti-cancer drugs, thus revealing a new mechanism by which tumor may be refractory to chemotherapy. miRNAs, such as miR-205, miR-200b and miR-34a, each regulating at least a couple of important players in different chemotherapy-relevant pathways, could prove particularly useful targets for developing strategies aimed at positively modulating chemosensitivity in PCa. However, since the role of these miRNAs has been mainly investigated in cell models, their actual involvement in the

chemosensitivity profile of PCa need to be properly defined in preclinical models, including orthotopic and patient-derived xenografts, which better recapitulate clinical PCa features.

Although further improvement in miRNA delivery strategies, in terms of increased efficiency and specificity of delivery to the target organ/tissue, is still necessary, the applicability of strategies aimed to modulate miRNA expression in the clinical setting is currently under investigation as the first liposome-formulated mimic of the tumor suppressor miR-34a (MRX34) recently entered Phase I clinical trial for patients with unresectable primary liver cancer and advanced or metastatic cancer with liver involvement (ClinicalTrials.gov Identifier: NCT01829971).

At present, nothing can be concluded concerning the possible relevance of miRNAs as novel biomarkers of treatment response. However, the possibility to carry studies encompassing large case series of patients, homogeneous for clinic-pathological characteristics will be instrumental for the identification and validation of specific miRNAs as predictive biomarkers for more precise stratification of patients according to their probability to respond to specific treatments.

LIST OF ABBREVIATIONS

AGO	=	Argonaute
CLL	=	B-cell chronic lymphocytic leukemia
DGCR8	=	DiGeorge syndrome critical region gene 8
EMT	=	Epithelial-to-mesenchymal transition
miRISC	=	miRNA-RNA inducing silencing complex
miRNA	=	microRNA
pri-miRNA	=	miRNA primary transcript
pre-miRNA	=	miRNA precursor
RNAa	=	RNA activation
XPO5	=	Exportin 5

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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REFERENCES

[1] Pasquinelli AE. MicroRNAs and their targets:recognition, regulation and an emerging reciprocal relationship. Nat Rev Genet 2012; 13: 271-82.

[2] Lee RC, Feinbaum RL, Ambros V. The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. Cell 1993; 75: 843-54.

[3] Carrington JC, Ambros V. Role of microRNAs in plant and animal development. Science 2003; 301: 336-8.

[4] Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. Cell 2004; 116: 281-97.

[5] Ambros V. The functions of animal microRNAs. Nature 2004; 431: 350-5.

[6] Ambros V. The evolution of our thinking about microRNAs. Nat Med 2008; 14: 1036-40.

[7] Plaisance-Bonstaff K, Renne R. Viral miRNAs. Methods Mol Biol 2011; 721: 43-66.

[8] Farazi TA, Hoell JI, Morozov P, Tuschl T. MicroRNAs in human cancer. Adv Exp Med Biol 2013; 774: 1-20.

[9] Finnegan EF, Pasquinelli AE. MicroRNA biogenesis: regulating the regulators. Crit Rev Biochem Mol Biol 2013; 48: 51-68.

[10] Fabian MR, Sonenberg N, Filipowicz W. Regulation of mRNA translation and stability by microRNAs. Annu Rev Biochem 2010; 79: 351-79.

[11] Cannistraci A, Di Pace AL, De Maria R, Bonci D. MicroRNA as new tools for prostate cancer risk assessment and therapeutic intervention: results from clinical data set and patients' samples. Biomed Res Int 2014; 2014: 146170.

[12] Zheng L, Wang L, Gan J, Zhang H. RNA activation: promise as a new weapon against cancer. Cancer Lett 2014; 355: 18-24.

[13] Vasudevan S, Tong Y, Steitz JA. Switching from repression to activation: microRNAs can up-regulate translation. Science 2007; 318: 1931-4.

[14] Calin GA, Dumitru CD, Shimizu M, *et al*. Frequent deletions and down-regulation of micro- RNA genes miR15 and miR16 at 13q14 in chronic lymphocytic leukemia. Proc Natl Acad Sci USA 2002; 99: 15524-9.

[15] Cimmino A, Calin GA, Fabbri M, *et al*. miR-15 and miR-16 induce apoptosis by targeting BCL2. Proc Natl Acad Sci USA 2005; 102: 13944-9. Erratum in: Proc Natl Acad Sci USA 2006; 103: 2464.

[16] De Cecco L, Dugo M, Canevari S, Daidone MG, Callari M. Measuring microRNA expression levels in oncology: from samples to data analysis. Crit Rev Oncog 2013; 18: 273-87.

[17] Santambrogio F, Gandellini P, Cimino-Reale G, Zaffaroni N, Folini M. MicroRNA-dependent regulation of telomere maintenance mechanisms: a field as much unexplored as potentially promising. Curr Pharm Des 2014; 20: 6404-21.

[18] Pang Y, Young CY, Yuan H. MicroRNAs and prostate cancer. Acta Biochim Biophys Sin (Shanghai) 2010; 42: 363-9.

[19] Folini M, Gandellini P, Longoni N, *et al*. miR-21: an oncomir on strike in prostate cancer. Mol Cancer 2010; 9: 12.

[20] Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin 2014; 64: 9-29.

[21] Perez BA, Koontz BF. Radiotherapy before and after radical prostatectomy for high-risk and locally advanced prostate cancer. Urol Oncol 2015; 33: 226-34.

[22] Seruga B, Ocana A, Tannock IF. Drug resistance in metastatic castration-resistant prostate cancer. Nat Rev Clin Oncol 2010; 8: 12-23.

[23] Suzman DL, Antonarakis ES. Castration-resistant prostate cancer: latest evidence and therapeutic implications. Ther Adv Med Oncol 2014; 6: 167-79.

[24] Sheikh H, Abdulghani J, Ali S, Sinha R, Lipton A. Impact of genetic targets on prostate cancer therapy. Adv Exp Med Biol 2013; 779: 359-83.

[25] Khatri N, Rathi M, Baradia D, Trehan S, Misra A. *In vivo* delivery aspects of miRNA, shRNA and siRNA. Crit Rev Ther Drug Carrier Syst 2012; 29: 487-527.

[26] Li Z, Rana TM. Therapeutic targeting of microRNAs: current status and future challenges. Nat Rev Drug Discov 2014; 13: 622-38.

[27] Jazbutyte V, Thum T. MicroRNA-21: from cancer to cardiovascular disease. Curr Drug Targets 2010; 11: 926-35.

[28] Chan JA, Krichevsky AM, Kosik KS. MicroRNA-21 is an antiapoptotic factor in human glioblastoma cells. Cancer Res 2005; 65: 6029-33.

[29] Dillhoff M, Liu J, Frankel W, Croce C, Bloomston M. MicroRNA-21 is overexpressed in pancreatic cancer and a potential predictor of survival. J Gastrointest Surg 2008; 12: 2171-6.

[30] Gramantieri L, Fornari F, Callegari E, *et al*. MicroRNA involvement in hepatocellular carcinoma. J Cell Mol Med 2008; 12: 2189-004.

[31] Iorio MV, Casalini P, Tagliabue E, Ménard S, Croce CM. MicroRNA profiling as a tool to understand prognosis, therapy response and resistance in breast cancer. Eur J Cancer 2008; 44: 2753-9.

[32] Schetter AJ, Leung SY, Sohn JJ, *et al*. MicroRNA expression profiles associated with prognosis and therapeutic outcome in colon adenocarcinoma. JAMA 2008; 299: 425-36.

[33] Yan LX, Huang XF, Shao Q, *et al*. MicroRNA miR-21 overexpression in human breast cancer is associated with advanced clinical stage, lymph node metastasis and patient poor prognosis. RNA 2008; 14: 2348-60.

[34] Zhang Z, Li Z, Gao C, *et al*. miR-21 plays a pivotal role in gastric cancer pathogenesis and progression. Lab Invest 2008; 88: 1358-66.

[35] Qi L, Bart J, Tan L, *et al*. Expression of miR-21 and its targets (PTEN, PDCD4, TM1) in flat epithelial atypia of the breast in relation to ductal carcinoma *in situ* and invasive carcinoma. BMC Cancer 2009; 9: 163.

[36] Seike M, Goto A, Okano T. MiR-21 is an EGFR-regulated anti-apoptotic factor in lung cancer in never-smokers. Proc Natl Acad Sci USA 2009; 106: 12085-90.

[37] Meng F, Henson R, Wehbe-Janek H, Ghoshal K, Jacob ST, Patel T. MicroRNA-21 regulates expression of the PTEN tumor suppressor gene in human hepatocellular cancer. Gastroenterology 2007; 133: 647-58.

[38] Zhu S, Si ML, Wu H, Mo YY. MicroRNA-21 targets the tumor suppressor gene tropomyosin 1 (TPM1). J Biol Chem 2007; 282: 14328-36.

[39] Asangani IA, Rasheed SA, Nikolova DA, *et al*. MicroRNA-21 (miR-21) post-transcriptionally downregulates tumor suppressor Pdcd4 and stimulates invasion, intravasation and metastasis in colorectal cancer. Oncogene 2008; 27: 2128-36.

[40] Volinia S, Calin GA, Liu CG, *et al*. A microRNA expression signature of human solid tumors defines cancer gene targets. Proc Natl Acad Sci USA 2006; 103: 2257-61.

[41] Ribas J, Lupold SE. The transcriptional regulation of miR-21, its multipletranscripts, and their implication in prostate cancer. Cell Cycle 2010; 9: 923-9.

[42] Ribas J, Ni X, Haffner M, *et al*. miR-21: an androgen receptor-regulated microRNA that promotes hormone-dependent and hormone-independent prostate cancer growth. Cancer Res 2009; 69: 7165-9.

[43] Hulf T, Sibbritt T, Wiklund ED, *et al*. Discovery pipeline for epigenetically deregulated miRNAs in cancer: integration of primary miRNA transcription. BMC Genomics 2011; 12: 54.

[44] Shi GH, Ye DW, Yao XD, *et al*. Involvement of microRNA-21 in mediating chemo-resistance to docetaxel in androgen-independent prostate cancer PC3 cells. Acta Pharmacol Sin 2010; 31: 867-73.

[45] Misso G, Di Martino MT, De Rosa G, *et al*. Mir-34: a new weapon against cancer? Mol Ther Nucleic Acids 2014; 3: e194.

[46] Welch C, Chen Y, Stallings RL. MicroRNA-34a functions as a potential tumor suppressor by inducing apoptosis in neuroblastoma cells. Oncogene 2007; 26: 5017-22.

[47] He C, Xiong J, Xu X, *et al*. Functional elucidation of MiR-34 in osteosarcoma cells and primary tumor samples. Biochem Biophys Res Commun 2009; 388: 35-40.

[48] Corney DC, Hwang CI, Matoso A, *et al*. Frequent downregulation of miR-34 family in human ovarian cancers. Clin Cancer Res 2010; 16: 1119-28.

[49] Fabbri M, Bottoni A, Shimizu M, *et al*. Association of a microRNA/TP53 feedback circuitry with pathogenesis and outcome of B-cell chronic lymphocytic leukemia. JAMA 2011; 305: 59-67.

[50] Vogt M, Munding J, Grüner M, *et al*. Frequent concomitant inactivation of miR-34a and miR-34b/c by CpG methylation in colorectal, pancreatic, mammary, ovarian, urothelial, and renal cell carcinomas and soft tissue sarcomas. Virchows Arch 2011; 458: 313-22.

[51] Mattie MN, Benz CC, Bowers J, *et al*. Optimized high-throughput microRNA expression profiling provides novel biomarker assessment of clinical prostate and breast cancer biopsies. Mol Cancer 2006; 5: 24.

[52] Ambs S, Prueitt RL, Yi M, *et al*. Genomic profiling of microRNA and messenger RNA reveals deregulated microRNA expression in prostate cancer. Cancer Res 2008; 68: 6162-70.

[53] Fujita Y, Kojima K, Hamada N, *et al*. Effects of miR-34a on cell growth and chemoresistance in prostate cancer PC3 cells. Biochem Biophys Res Commun 2008; 377: 114-9.

[54] Liu C, Kelnar K, Liu B, *et al*. The microRNA miR-34a inhibits prostate cancer stem cells and metastasis by directly repressing CD44. Nat Med 2011; 17: 211-6.

[55] Corcoran C, Rani S, O'Driscoll L. miR-34a is an intracellular and exosomal predictive biomarker for response to docetaxel with clinical relevance to prostate cancer progression. Prostate 2014; 74: 1320-34.

[56] Kojima K, Fujita Y, Nozawa Y, Deguchi T, Ito M. MiR-34a attenuates paclitaxel-resistance of hormone-refractory prostate cancer PC3 cells throughdirect and indirect mechanisms. Prostate 2010; 70: 1501-12.

[57] Rokhlin OW, Scheinker VS, Taghiyev AF, Bumcrot D, Glover RA, Cohen MB. MicroRNA-34 mediates AR-dependent p53-induced apoptosis in prostate cancer. Cancer Biol Ther 2008; 7: 1288-96.

[58] Lee YS, Kim HK, Chung S, Kim KS, Dutta A. Depletion of human micro-RNA miR-125b reveals that it is critical for the proliferation of differentiated cells but not for the down-regulation of putative targets during differentiation. J Biol Chem 2005; 280: 16635-41.

[59] Yu-Meng S, Kang-Yu L, Yue-Qin C. Diverse functions of miR-125 family in different cell contexts. J Hematol Oncol 2013; 6: 6.

[60] Ueda T, Volinia S, Okumura H, *et al*. Relation between microRNA expression and progression and prognosis of gastric cancer: a microRNA expression analysis. Lancet Oncol 2010; 11: 136-46.

[61] Baffa R, Fassan M, Volinia S, *et al*. MicroRNA expression profiling of human metastatic cancers identifies cancer gene targets. J Pathol 2009; 219: 214-21.

[62] Bloomston M, Frankel WL, Petrocca F, *et al*. MicroRNA expression patterns to differentiate pancreatic adenocarcinoma from normal pancreas and chronic pancreatitis. JAMA 2007; 297: 1901-8.

[63] Veerla S, Lindgren D, Kvist A, *et al*. MiRNA expression in urothelial carcinomas: important roles of miR-10a, miR-222, miR-125b, miR-7 and miR-452 for tumor stage and metastasis, and frequent homozygous losses of miR-31. Int J Cancer 2009; 124: 2236-42.

[64] Sorrentino A, Liu CG, Addario A, Peschle C, Scambia G, Ferlini C. Role of microRNAs in drugresistant ovarian cancer cells. Gynecol Oncol 2008; 111: 478-86.

[65] Sonoki T, Iwanaga E, Mitsuya H, Asou N. Insertion of microRNA-125b-1, a human homologue of lin-4, into a rearranged immunoglobulin heavy chain gene locus in a patient with precursor B-cell acute lymphoblastic leukemia. Leukemia 2005; 19: 2009-10.

[66] Nelson PT, Baldwin DA, Kloosterman WP, Kauppinen S, Plasterk RH, Mourelatos Z. RAKE and LNA-ISH reveal microRNA expression and localization in archival human brain. RNA 2006; 12: 187-91.

[67] Gefen N, Binder V, Zaliova M, *et al*. Hsa-mir-125b-2 is highly expressed in childhood ETV6/RUNX1 (TEL/AML1) leukemias and confers survival advantage to growth inhibitory signals independent of p53. Leukemia 2010; 24: 89-96.

[68] Porkka KP, Pfeiffer MJ, Waltering KK, Vessella RL, Tammela TL, Visakorpi T. MicroRNA expression profiling in prostate cancer. Cancer Res 2007; 67: 6130-5.

[69] Shi XB, Xue L, Yang J, *et al*. An androgen-regulated miRNA suppresses Bak1 expression and induces androgen-independent growth of prostate cancer cells. Proc Natl Acad Sci USA 2007; 104: 19983-8.

[70] Mitchell PS, Parkin RK, Kroh EM, *et al*. Circulating microRNAs as stable blood-based markers for cancer detection. Proc Natl Acad Sci USA 2008; 105: 10513-8.

[71] Prueitt RL, Yi M, Hudson RS, *et al*. Expression of microRNAs and protein-coding genes associated with perineural invasion in prostate cancer. Prostate 2008; 68: 1152-64.

[72] Shi XB, Xue L, Ma AH, Tepper CG, Kung HJ, White RW. miR-125b promotes growth of prostate cancer xenograft tumor through targeting pro-apoptotic genes. Prostate 2011; 71: 538-49.

[73] Amir S, Ma A, Shi XB, Xue L, Kung HJ, deVere White RW. Oncomir miR-125b suppresses p14ARF to modulate p53-dependent and p53-independent apoptosis in prostate cancer. PLoS One 2013; 8: e61064.

[74] Bemis DL, Capodice JL, Desai M, Buttyan R, Katz AE. A concentrated aglycone isoflavone preparation (GCP) that demonstrates potent anti-prostate cancer activity *in vitro* and *in vivo*. Clin Cancer Res 2004; 10: 5282-92.

[75] Michael MZ, O' Connor SM, van Holst Pellekaan NG, Young GP, James RJ. Reduced accumulation of specific microRNAs in colorectal neoplasia. Mol Cancer Res 2003; 1: 882-91.

[76] Iorio MV, Ferracin M, Liu CG, *et al*. MicroRNA gene expression deregulation in human breast cancer. Cancer Res 2005; 65: 7065-70.

[77] Gao W, Yu Y, Cao H, *et al*. Deregulated expression of miR-21, miR-143 and miR-181a in non-small cell lung cancer is related to clinicopathologic characteristics or patient prognosis. Biomed Pharmacother 2010; 64: 399-408.

[78] Zhang H, Cai X, Wang Y, Tang H, Tong D, Ji F. MicroRNA-143, down-regulated in osteosarcoma, promotes apoptosis and suppresses tumorigenicity by targeting Bcl-2. Oncol Rep 2010; 24: 1363-9.

[79] Zhang N, Su Y, Xu L. Targeting PKCε by miR-143 regulates cell apoptosis in lung cancer. FEBS Lett 2013; 587: 3661-7.

[80] Yan X, Chen X, Liang H, *et al*. miR-143 and miR-145 synergistically regulate ERBB3 to suppress cell proliferation and invasion in breast cancer. Mol Cancer 2014; 13: 220.

[81] Clapé C, Fritz V, Henriquet C, *et al*. miR-143 interferes with ERK5 signaling, and abrogates prostate cancer progression in mice. PLoS One 2009; 4: e7542.

[82] Szczyrba J, Loprich E, Wach S, *et al*. The microRNA profile of prostate carcinoma obtained by deep sequencing. Mol Cancer Res 2010; 8: 529-38.

[83] Ahmad I, Singh LB, Yang ZH, *et al*. Mir143 expression inversely correlates with nuclear ERK5 immunoreactivity in clinical prostate cancer. Br J Cancer 2013; 108: 149-54.

[84] Xu B, Niu X, Zhang X, *et al*. miR-143 decreases prostate cancer cells proliferation and migration and enhances their sensitivity to docetaxel through suppression of KRAS. Mol Cell Biochem 2011; 350: 207-13.

[85] Chen Y, Song YX, Wang ZN. The microRNA-148/152 family: multi-faceted players. Mol Cancer 2013; 12: 43.

[86] Mattie MD, Benz CC, Bowers J, *et al*. Optimized high-throughput microRNA expression profiling provides novel biomarker assessment of clinical prostate and breast cancer biopsies. Mol Cancer 2006; 5: 24.

[87] Fujita Y, Kojima K, Ohhashi R, *et al*. MiR-148a attenuates paclitaxel resistance of hormone-refractory, drug-resistant prostate cancer PC3 cells by regulating MSK1 expression. J Biol Chem 2010; 285: 19076-84.

[88] Feng X, Wang Z, Fillmore R, Xi Y. MiR-200, a new star miRNA in human cancer. Cancer Lett 2014; 344: 166-73.

[89] Kong D, Li Y,Wang Z, *et al*. miR-200 regulates PDGF-D-mediated epithelial-mesenchymal transition, adhesion, and invasion of prostate cancer cells. Stem Cells 2009; 27: 1712-21.

[90] Banyard J, Chung I, Wilson AM, *et al*. Regulation of epithelial plasticity by miR-424 and miR-200 in a new prostate cancer metastasis model. Sci Rep 2013; 3: 3151.

[91] Kim J, Wu L, Zhao JC, Jin HJ, Yu J. TMPRSS2-ERG gene fusions induce prostate tumorigenesis by modulating microRNA miR-200c. Oncogene 2013; 33: 5183-92.

[92] Yu J, Lu Y, Cui D, *et al*. miR-200b suppresses cell proliferation, migration and enhances chemosensitivity in prostate cancer by regulating Bmi-1. Oncol Rep 2014; 31: 910-8.

[93] Williams LV, Veliceasa D, Vinokour E, Volpert OV. miR-200b inhibits prostate cancer EMT, growth and metastasis. PLoS One 2013; 8: e83991.

[94] Puhr M, Hoefer J, Schäfer G, *et al*. Epithelial-to-mesenchymal transition leads to docetaxel resistance in prostate cancer and is mediated by reduced expression of miR-200c and miR-205. Am J Pathol 2012; 181: 2188-201.

[95] Gottardo F, Liu CG, Ferracin M, *et al*. Micro-RNA profiling in kidney and bladder cancers. Urol Oncol 2007; 25: 387-92.

[96] Iorio MV, Visone R, Di Leva G, *et al*. MicroRNA signatures in human ovarian cancer. Cancer Res 2007; 67: 8699-7.

[97] Feber A, Xi L, Luketich JD, *et al*. MicroRNA expression profiles of esophageal cancer. J Thorac Cardiovasc Surg 2008; 135: 255-60.

[98] Sempere LF, Christensen M, Silahtaroglu A, *et al*. Altered MicroRNA expression confined to specific epithelial cell subpopulations in breast cancer. Cancer Res 2007; 67: 11612-20.

[99] Gandellini P, Folini M, Longoni N, *et al*. miR-205 Exerts tumor-suppressive functions in human prostate through down-regulation of protein kinase Cepsilon. Cancer Res 2009; 69: 2287-95.

[100] Majid S, Dar AA, Saini S, *et al*. MicroRNA-205-directed transcriptional activation of tumor suppressor genes in prostate cancer. Cancer 2010; 116: 5637-49.

[101] Schaefer A, Stephan C, Busch J, Yousef GM, Jung K. Diagnostic, prognostic and therapeutic implications of microRNAs in urologic tumors. Nat Rev Urol 2010; 7: 286-97.

[102] Verdoodt B, Neid M, Vogt M, *et al*. MicroRNA-205, a novel regulator of the anti-apoptotic protein Bcl2, is downregulated in prostate cancer. Int J Oncol 2013; 43: 307-14.

[103] Wang N, Li Q, Feng NH, *et al*. miR-205 is frequently downregulated in prostate cancer and acts as a tumor suppressor by inhibiting tumor growth. Asian J Androl 2013; 15: 735-41.

[104] Gandellini P, Rancati T, Valdagni R, Zaffaroni N. miRNAs in tumor radiation response: bystanders or participants? Trends Mol Med 2014; 20: 529-39.

[105] Bhatnagar N, Li X, Padi SK, Zhang Q, Tang MS, Guo B. Down-regulation of miR-205 and miR-31 confers resistance to chemotherapy-induced apoptosis in prostate cancer cells. Cell Death Dis 2010; 1: e105.

[106] Schaefer A, Jung M, Mollenkopf HJ, *et al*. Diagnostic and prognostic implications of microRNA profiling in prostate carcinoma. Int J Cancer 2010; 126: 1166-76.

[107] Hagman Z, Haflidadottir BS, Ceder JA, *et al*. miR-205 negatively regulates the androgen receptor and is associated with adverse outcome of prostate cancer patients. Br J Cancer 2013; 108: 1668-76.

[108] Kalogirou C, Spahn M, Krebs M, *et al*. MiR-205 is progressively down-regulated in lymph node metastasis but fails as a prognostic biomarker in high-risk prostate cancer. Int J Mol Sci 2013; 14: 21414-34.

[109] Gandellini P, Profumo V, Casamichele A, *et al*. miR-205 regulates basement membrane deposition in human prostate: implications for cancer development. Cell Death Differ 2012; 19: 1750-60.

[110] Gandellini P, Giannoni E, Casamichele A, *et al*. miR-205 hinders the malignant interplay between prostate cancer cells and associated fibroblasts. Antioxid Redox Signal 2013; 20: 1045-59.

[111] Thiery JP, Sleeman JP. Complex networks orchestrate epithelial-mesenchymal transitions. Nat Rev Mol Cell Biol 2006; 7: 131-42.

[112] Voulgari A, Pintzas A. Epithelial-mesenchymal transition in cancer metastasis: mechanisms, markers and strategies to overcome drug resistance in the clinic. Biochim Biophys Acta 2009; 1796: 75-90.

[113] Pennati M, Lopergolo A, Profumo V, *et al*. miR-205 impairs the autophagic flux and enhances cisplatin cytotoxicity in castration-resistant prostate cancer cells. Biochem Pharmacol 2014; 87: 579-97.

[114] Klionsky DJ, Abdalla FC, Abeliovich H, *et al*. Guidelines for the use and interpretation of assays for monitoring autophagy. Autophagy 2012; 8: 445-4.

[115] Sita-Lumsden A, Fletcher CE, Dart DA, Brooke GN, Waxman J, Bevan CL. Circulating nucleic acids as biomarkers of prostate cancer. Biomark Med 2013; 7: 867-77.

[116] Zhang HL, Yang LF, Zhu Y, *et al*. Serum miRNA-21: elevated levels in patients with metastatic hormone-refractory prostate cancer and potential predictive factor for the efficacy of docetaxel-based chemotherapy. Prostate 2011; 71: 326-31.

[117] Lin HM, Castillo L, Mahon KL, *et al*. Circulating microRNAs are associated with docetaxel chemotherapy outcome in castration-resistant prostate cancer. Br J Cancer 2014; 110: 2462-71.

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