Mechanisms of docetaxel resistance in prostate cancer: the key role played by miRNAs

Milena Rizzo[1]

[1]Non-coding RNA group, Functional Genetics and Genomics lab, Institute of Clinical Physiology (IFC), CNR, Pisa, Italy; milena.rizzo@ifc.cnr.it

Corresponding Author address:

Dr. Milena Rizzo

Non-coding RNA group

Functional Genetics and Genomics lab

Institute of Clinical Physiology (IFC), CNR

via Moruzzi 1, 56124 Pisa, Italy

Tel.: +39 050 3153107

Fax: +39 050 3153327

milena.rizzo@ifc.cnr.it

ABSTRACT

One of the main problems with the treatment of metastatic prostate cancer is that, despite an initial positive response, the majority of patients develop resistance and progress. In particular, the resistance to docetaxel, the gold standard therapy for metastatic prostate cancer since 2010, represents one of the main factors responsible for the failure of prostate cancer therapy. According to the present knowledge, different processes contribute to the appearance of docetaxel resistance and non-coding RNA seems to play a relevant role in them. In this review, a comprehensive overview of the miRNA network involved in docetaxel resistance is described, highlighting the pathway/s affected by their activity.

Keywords: miRNAs, docetaxel resistance, prostate cancer, drug resistance, taxane

1. Introduction

Prostate cancer (PCa) is the second most frequent cancer in men [1]. Despite the high long-term survival in localized PCa, metastatic PCa remains largely incurable. One of the main problems when PCa progress from localized to advanced disease is that patients who initially benefit from a specific treatment commonly become refractory to therapy. The treatment for advanced PCa initially consists of androgen deprivation therapies (ADT) achieved by surgical castration (orchiectomy) or chemical castration using agents targeting androgen receptor (AR) signaling (e.g. AR antagonist, gonadotropin-releasing hormone agonist, etc.) [2]. Unfortunately, a high percentage of patients, after an initial positive response, experience recurrence and become insensitive to ADT and progress to a second phase named castration resistant prostate cancer (CRPC). Since 2010, the gold standard therapy for CRPC was docetaxel (DCT) chemotherapy [3-5] in combination with the second-generation anti-androgens such as enzalutamide or inhibitors of androgen biosynthesis such as abiraterone [6-8]. Even though the use of these drugs has improved clinical outcomes prolonging the lifespan, many patients develop resistance. Although the exact molecular mechanisms of DCT resistance are not completely clarified, in the last few years several lines of evidence have highlighted the important role that microRNAs (miRNAs) play in the sensitivity to this drug. miRNAs are small single stranded RNA molecules that have a fundamental role in the regulation of gene expression at the post-transcriptional level in all physiological and pathological aspects of cell biology. miRNAs that play a role in DCT resistance in PCa were last summarized in 2015 [9] and partially addressed by Li et al. [10] and Razdan et al. [11]. Recently several new miRNAs have been identified contributing to this phenomenon.

The aim of this review is to outline the miRNAs that have to date been demonstrated to counteract or increase DCT resistance in PCa pointing out the mechanisms whereby they exert their role.

2. Mechanisms of docetaxel resistance in Prostate Cancer

2.1. Mechanisms of docetaxel action

DCT is a second-generation chemotherapeutic drug of the taxane family. At the molecular level it binds with high affinity to β-tubulin disrupting microtubule dynamics and thereby affecting cytoskeleton functions during mitosis. As a consequence, the normal progression of the cell cycle is impaired resulting in G2/M arrest leading to inhibition of proliferation and cell death [12].

Despite their mitotic function, taxanes have also been reported to affect non-mitotic functions such as alterations of several signaling pathways or inhibition of intracellular trafficking [13]. It has been shown that DCT induces apoptosis via BCL2 phosphorylation followed by caspase activation [14, 15] or inhibits cell proliferation by downregulating ERK1/2 signaling [16]. Moreover, taxanes inhibit ligand-induced AR nuclear translocation and hence the downstream activation of AR target genes [17, 18].

2.2. Mechanisms of docetaxel resistance

In this section the main mechanisms of DCT resistance are described, discussing in greater detail the ones in which miRNAs involved in DCT resistance exert a regulatory role.

The more consolidated mechanisms of DCT resistance in PCa are (Fig. 1):

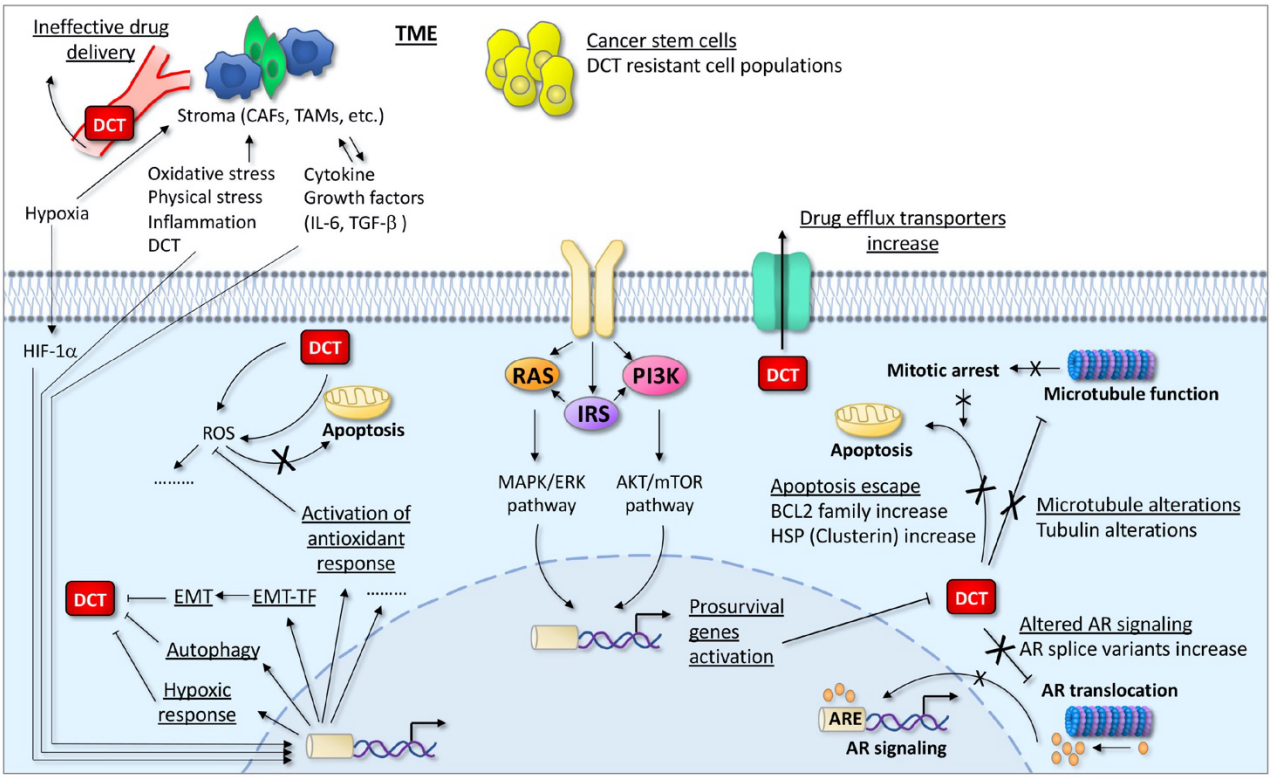

Figure 1. Schematic overview of the mechanisms of DCT resistance in PCa. AR, androgen receptor; ARE, androgen response element; CAF, cancer-associated fibroblasts; DCT, docetaxel; EMT, epithelial mesenchymal transition; EMT-TF, epithelial mesenchymal transition transcription factors; ROS, Reactive oxygen species; TAM, tumor-associated macrophage; TME, tumor microenvironment.

Alterations of microtubule. It has been reported that structural/functional alterations of microtubule targeted by DCT have an impact on drug efficacy [19, 20]. Upregulation of βIII-tubulin [21, 22] as well as mutations of the β- or α-tubulin genes [23] or modifications of the microtubule-associated proteins [24] can modify either the microtubule dynamics (βIII-tubulin-containing microtubules are less stable and exhibit aberrant dynamics) or the DCT binding capability. As a consequence, cancer cells become less sensitive to DCT toxicity.

Drug efflux transporter upregulation. The ATP-binding cassette (ABC) transporters are a superfamily of drug efflux pumps involved in the transmembrane transport of intracellular substrates [25]. Some members of this family present a broad drug specificity and are involved in drug resistance as they extrude the drugs resulting in a decrease of the intracellular drug concentration and hence their ability to target the cells [19, 20]. Indeed, the upregulation of some members of this family such as ABCB1

(MDR1), ABCC1 (MRP1) and ABCC4 (MRP4) has been associated with DCT resistance in PCa by increasing DCT extrusion [26-29].

In addition, several other pathways have been associated to DCT resistance in PCa.

Survival pathways activation/apoptosis escape. Deregulation of several proteins involved in signaling pathways that increase tumor cells survival or that allow cells to evade apoptosis are associated to DCT resistance in PCa. It has been shown that antiapoptotic proteins belonging to the BCL2 family such as BCL-2, BCL-XL and MCl-1 are associated with DCT resistance probably by affecting the homodimerization of BAX or BAK proapoptotic proteins and hence the DCT-induced apoptosis process [30, 31]. Indeed, the inhibition of the BCL2 family sensitizes PCa cells to DCT [32, 33]. The upregulation of chaperon molecules such as Clusterin, Hsp27 and Hsp90 has also been associated with DCT resistance [31, 34]. In particular, Clusterin exerts a key role in preventing apoptosis induced by cytotoxic drugs (such as DCT) by sequestering BAX [35, 36]. Some therapeutic approaches based on targeting Clusterin are under evaluation [37]. Docetaxel resistance was also found to be associated with PAR1 activation that reduce DCT-induced apoptosis by NF-Kβ activation [38]. Several pathways associated with PCa cell survival have also been linked to DCT resistance. Activation of the PI3K/AKT pathway is often observed when PCa progresses toward a resistant disease and even in this case therapeutic approaches targeting this signal pathway have shown promising results [39-41]. In the same way the MAPK/ERK pathway is also activated in DCT resistant (DCT^R) PCa cells and plays a role in DCT resistance [16, 42, 43]. Vidal et al. identified GATA2 as a regulator of chemotherapy resistance in PCa [44, 45]. Authors demonstrated that GATA2 acts as a transcriptional activator of IGF-2 that in turn activates IGF-1R and INS-R and the downstream signal pathways leading to cell proliferation and survival. Finally, also Notch, Hedgehog, JNK and WNT/β-Catenin signaling pathways have been associated to DCT resistance [19, 31, 46].

Altered AR signaling. As previously explained (paragraph 2.1), DCT affects AR signaling by altering microtubule-associated AR nuclear translocation. Indeed, it has been demonstrated that DCT does not impair the nuclear accumulation of AR splice variants (such as AR-V7) [47] and that AR-V7 is

upregulated in DCT^R PCa cell lines [48]. However, the impact of AR splice variants on DCT resistance is a matter of debate [49].

Activation of antioxidant response. Taxanes have been shown to trigger reactive oxygen species (ROS) formation in cancer cells. An excessive ROS concentration may lead to apoptosis activation [50] contributing to the toxicity of taxanes [51]. It has been shown that paclitaxel induces alterations in the mitochondrial membrane that affect cytochrome C release and reactive oxygen species (ROS) production leading to apoptosis [52]. In turn, in response to taxanes-induced ROS production, cancer cells activate an antioxidant response that enables cells to resist the cytotoxicity of taxanes [50, 53]. Indeed, the upregulation of antioxidant enzymes has been associated to DCT resistance. Zhang et al. reported that high BIM-1 expression, that predicts poor prognosis in PCa patients, increases DCT resistance by activating an antioxidant response that reduces ROS and cell death [50]. Intriguingly, it has been shown that the antioxidant response and the consequent ROS decrease mediated DCT resistance by also activating pro-survival pathways. Indeed, Zhang et al. demonstrated that high SOD2 level in DCT^R cells determined a ROS reduction that in turn impaired the arrestin-1 dependent insulin-like growth factor-I receptor (IGF-1R) degradation [54]. IGF-1 signaling is believed to play a prominent role in tumor growth and drug resistance [55].

The DCT resistance, and in general taxanes resistance, is a complex phenomenon dependent on the activation of several molecular pathways both in cancer cells and in the surrounding tumor microenvironment (TME). The TME is characterized by aberrant angiogenesis and hence by a chaotic blood flow that not only impairs drug distribution but also the delivery of oxygen and nutrients, generating regions of tumor hypoxia that contribute to taxanes resistance [30, 56]. Indeed, hypoxia triggers the activation of the hypoxia-inducible factor 1α (HIF-1α) that in turn activates the so-called hypoxic response and several HIF-1α dependent pathways such as autophagy and epithelial to mesenchymal transition (EMT) [57, 58]. All these pathways, including the hypoxic response [57, 59, 60], contribute to taxanes resistance (see below). The TME is also characterized by the presence of cytokines and growth factors (such as IL-6, TGF-β) produced by the cells of the tumor stroma (such

as tumor-associated macrophages (TAMs) and the cancer-associated fibroblasts (CAFs)) that further reinforce the activation of the above-mentioned pathways enhancing resistance [30, 56, 57].

Autophagy induction. Although autophagy is a process that in normal condition has a protective role as it facilitates the removal of harmful protein aggregates and cellular components, in cancer cells it can support growth and survival and so it is responsible for cancer progression and drug resistance [61]. Several lines of evidence demonstrated that an increased activation of autophagy supports DCT resistance in PCa [62-65]. E.g. upregulation of either FOXM1 [66] or NPRL2 [67] induces an autophagy-dependent DCT resistance through the regulation of the AMPK/mTOR pathway in PCa.

Epithelial to mesenchymal transition (EMT). Recently, an increasing number of reports support the involvement of the reactivation of EMT in the chemoresistance of cancer cells [58, 68]. Empirical evidence suggested that cells undergoing EMT acquire stem cell-like property, thus sharing key signaling pathways and the drug resistance phenotype with cancer stem cells (CSCs) (see below) [69, 70]. EMT implies a transcriptional reprogramming driven by specific transcription factors (EMT-TFs) whose activation is likely to be linked to cellular stemness and hence to drug resistance. Moreover, it has become clear that EMT-TFs (such as SNAI, TWIST and ZEB families) might have a non-EMT dependent effects playing a role in several drug resistance pathways such as i) inhibition of proapoptotic/activation of prosurvival pathways, ii) induction of drug detoxifying enzymes and iii) induction of drug efflux pumps (ABCB transporters) [58]. EMT markers are associated with PCa worst prognosis [71, 72]. Marin-Aguilera et al. demonstrated that DCT^R PCa cells express high EMT and stem-like cell markers [73]. They also proved that DCT treatment determined the enrichment of a subpopulation of PCa cells with EMT/stem-like gene expression signature that was less sensitive to DCT. Finally, they demonstrated that the ZEB1 silencing was able to revert the EMT/stem-like genes expression (restored CDH1 and suppressed CD44 expression) and, as a consequence, to decrease DCT resistance. ZEB1 plays a key role in drug resistance [74]. Its role in DCT resistance was confirmed by Hanrahan et al. who demonstrated that ZEB1, is a driver of EMT and DCT resistance in PCa through E-cadherin repression [75]. Finally, ZEB1 expression can confer DCT resistance by

modulating the drug efflux pump MRP4 expression [76], suggesting a non-EMT dependent role of EMT-TFs in PCa DCT resistance.

Cancer stem cells (CSC). The existence of a subpopulation of cancer cells with stemness characteristics (such as self-renewal) has been associated to drug resistance. CSCs, situated in a specialized microenvironment (niche) that contributed to their formation and maintenance, present/acquire several properties that enable them to resist to drug treatment [77, 78]. In particular, these properties are: I) high survival capacity (due to active DNA damage response systems, anti-apoptotic/pro-proliferative molecules activation and high telomerase activity); II) the ability to adopt a quiescent status; III) elevated drug export due to the high expression/activity of the drug efflux pumps; IV) low level ROS maintenance; V) stemness induction (due to EMT/stem-like pathways activation) [78]. Evidence suggested that DCT^R PCa cells and tissues are characterized by the increased presence of $CD44^+$ and/or $CD133^+$ CSC cells able to resist DCT toxicity by activating specific signaling pathway. It has been shown that the increased CD44 in DCT^R PCa cells promotes migration and invasion via induction of the HIPPO-YAP signaling pathway [79]. Talukdar et al. isolated prostate cancer stem cells (characterized by the expression of CD44/CD133 and self-renewal associated genes) and demonstrated that these cells were resistant to DCT [80]. The DCT resistance was due to the MDA-9 dependent activation of both STAT3 and NOTCH/cMYC pathways that determined the ABCB1 transporter upregulation with the consequent increase of drug efflux. The efficacies of prostate CSC eradication in reverting DCT resistance was demonstrated in vitro by several studies with different compounds [81, 82] including STAT3 inhibitors [83, 84].

3. Role of miRNAs in the mechanisms of docetaxel resistance

An increasing number of miRNAs have been discovered to play a role in the appearance of DCT resistance. Here, the miRNAs that play a role in PCa DCT resistance are described discussing the mechanism in which they are involved (Fig. 2, Table 1).

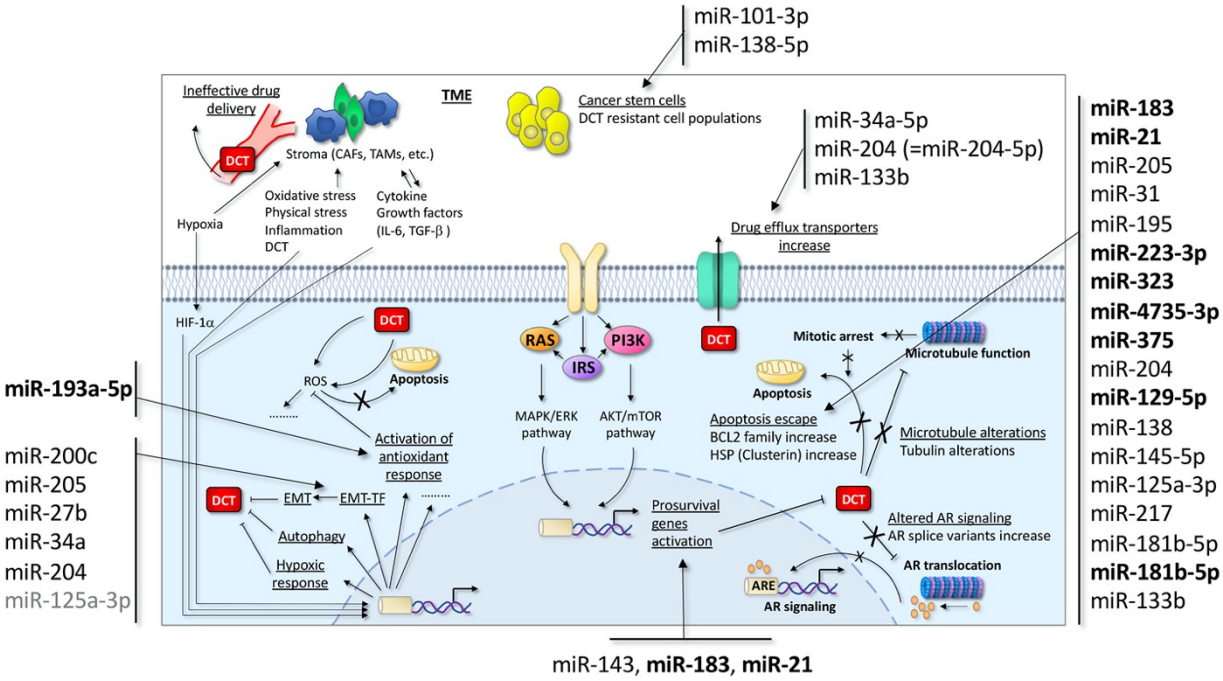

Figure 2. Schematic overview of the miRNAs involved in the mechanisms of PCa DCT resistance. miRNAs are grouped according to their role in DCT resistance. miRNAs that increase the DCT resistance are indicated in bold whereas miRNAs that sensitize cells to DCT are indicated in normal text. miRNA ID of the reference paper is indicated in the figure. miR-204 was reported with two different IDs (one in brackets) as its involvement in drug efflux transporters regulation was demonstrated by two different papers that use different miRNA ID. miR-125p is in grey as the authors only hypothesized its involvement in EMT.

3.1. Survival pathways activation/apoptosis escape

Several miRNAs affect DCT sensitivity by targeting genes that inhibit apoptosis or activate prosurvival pathways. Niu et al. demonstrated that insulin-like growth factor-I (IGF-1) induces DCT resistance in PCa cells by downregulating miR-143 expression [85]. Indeed, miR-143 downregulation induced by IGF-1 leads to the derepression of the miR-143 targets IGF-1 receptor (IGF-1R) and insulin receptor substrate 1 (IRS1). The consequent activation of the downstream signaling molecules (such as the transcription of the vascular endothelial growth factor, VEGF) determines DCT resistance through activation of prosurvival pathways. Indeed, miR-143 overexpression sensitizes PCa cells to DCT both *in vitro* and *in vivo*. The miR-143 ability to enhance DCT sensitivity in PCa was previously demonstrated by Xu et al., identifying the miR-143 direct target KRAS as the possible

mediator of miR-143 activity [86]. miR-183 is involved in PCa DCT resistance by regulating cell survival pathways [87]. It is indeed involved in a regulatory circuit together with lncRNA CASC2 and SPRY2: the overexpression of both mRNAs increase DCT sensitivity, mainly by affecting DCT-induced decrease of cell viability and apoptosis of PCa cells. In particular, CASC2 acts as a competing endogenous RNA (ceRNA) of miR-183 that in turn determines the derepression of its direct target SPRY2. SPRY2 is a well-known receptor tyrosine kinase (RTK) inhibitor [88] and the authors demonstrated that CASC2 overexpression inhibited ERK signaling and that this inhibition is partially attenuated by SPRY silencing [87]. Finally, Shi et al. demonstrated that miR-21 is highly expressed in PCa DCT^R cells and its knock down *in vitro* model increased DCT sensitivity through its target PDCD4 [89]. Indeed, miR-21 silencing or PDCD4 overexpression inhibited cell proliferation and increased apoptosis in DCT^R cells [89]. Intriguingly, a more recent paper demonstrated that miR-21 is regulated by IL-6 and that IL-6 inhibits PDCD4 through miR-21 activation [90]: these data support the association between IL-6 secretion and DCT resistance in PCa [91].

Regarding escape of apoptosis, some miRNAs play a role in DCT sensitivity by regulating antiapoptotic proteins. miR-205 and miR-31 are downregulated in DCT^R PCa cells and their overexpression increases DCT sensitivity by inhibiting the antiapoptotic BCL-W and E2F6 respectively thus promoting DCT-induced apoptosis [92]. In a later paper the same authors demonstrated that miR-205 downregulation, caused by promoter hypermethylation, determined the derepression of its target EZH2 [93]. EZH2, in turn, induced miR-31 promoter hypermethylation and, as a consequence, miR-31 downregulation. Therefore, the EZH2-dependent epigenetic silencing of miR-205/-31 plays a role in the mechanism of PCa DCT resistance, consistent with the positive correlation between high expression EZH2 level and PCa progression [94]. Similarly, miR-195 is downregulated in DCT^R PCa cells, and its overexpression promotes DCT-induced apoptosis by inhibiting its direct target clusterin, which is known to play a role in the apoptosis-avoidance mechanism of DCT resistance [95]. miRNAs also affected DCT-induced apoptosis by regulating proteins that have multiple roles beside apoptosis. miR-223-3p attenuated the DCT-induced apoptosis

directly regulating FOXO3 [96]. FOXO proteins are a family of transcription factors implicated in the regulation of cellular homeostasis (including apoptosis) and chemoresistance. Also miR-323 decrease the DCT-induced apoptosis probably through its direct target p73, which is a tumor suppressor belonging to the p53 family that modulates several aspects of tumor biology including drug resistance [97]. Similarly, miR-4735-3p, probably by inhibiting MEKK1 expression, may suppress DCT-induced apoptosis allowing PCa cells survival [98]. Finally, Wang et al. demonstrated that high miR-375 levels confer DCT resistance by decreasing apoptosis both in PCa *in vitro* and in a xenograft model [99]. The authors identified SEC23A and YAP1 as possible miR-375 targets mediators in DCT resistance.

Some studies discovered miRNAs that influence DCT resistance by inducing/repressing apoptosis even though they did not identify the target/s mediator/s. Lin et al. screened 1280 miRNAs (by miRNAs mimic transfection) in PCa cells treated with DCT and found that miR-217 and miR-181b-5p mimic enhanced DCT-induced apoptosis [100]. On the contrary, miR-181a was upregulated in DCT^R PCa cells and its inhibition in these cells increased apoptosis possibly by increasing p53 phosphorylation [101].

Finally, several miRNAs are involved in DCT resistance by affecting other mechanisms in addition to apoptosis. miR-204, that is downregulated in DCT^R PCa cells and chemoresistant PCa tissues, if overexpressed, sensitized cells to DCT and promoted apoptosis, at least in part, by inhibiting ZEB1 [102]. It is known that ZEB1 plays a crucial role in inhibiting apoptosis [103, 104] but the authors also discussed the master role of ZEB1 (and miR-204) in EMT and EMT driven drug resistance (paragraph 2.2). In addition, a previous work identified miR-204 as a part of a circuit involved in PCa DCT resistance [105]. More precisely, miR-204 is sponged by the lncRNA UCA1 and regulated SIRT1 in PCa. The SIRT1 upregulation due to UCA1 overexpression (that determines miR-204 sequestration/SIRT1 release) has been shown to promote DCT resistance by decreasing DCT-induced apoptosis (through caspase 3 activation) and by increasing ABCB1 (MDR1) expression. Wu et al. demonstrated that miR-129-5p, through the inhibition of CAMK2N1, attenuates

DCT efficacy not only by decreasing apoptosis (due to BCL2 induction and BAX repression) but also by increasing cell survival (with an increase of p-ERK1/2 and p-MEK) and invasion/migration potential of PCa cells [106]. miR-138 enhanced DCT resistance in PCa cells by inhibiting DCT-induced apoptosis and increasing integrin β1-mediated cells spreading in PCa cells [107]. Authors demonstrated that miR-138 overexpression, by targeting KINDLIN-2, enhances DCT-induced apoptosis. KINDLIN-2 is a member of a protein family whose members are key regulators of the adhesive function mediated by integrin. Indeed, the downregulation of KINDLIN-2, acting on β1 integrin, reinforces the reduction of cells spreading induced by DCT. The cell spreading downstream of β1 integrin signaling has been shown to promote chemoresistance [108, 109]. Xue et al. demonstrated that the lncRNA MALAT1 enhances DCT resistance in PCa cells by miR-145-5p-mediated regulation of AKAP12 [110]. The authors proved the existence of this axis in DCT^R PCa cells and, by modulating all the component of the axis, they demonstrated that MALAT1, via miR-145-5p/AKAP12, plays a role in apoptosis and in the migratory/invasive capability of DCT^R PCa cells. Ectopic expression of miR-133b promoted DCT-induced apoptosis (by BLC2/survivin decrease and BAX/cleaved caspase 3 decrease) and ABCG2 (MXR) expression [111]. The target mediator of the miR-133b activity is human antigen R (HuR). HuR is a RNA-binding protein that regulate the stability, translation and nucleus-to-cytoplasm translocation of its target mRNAs [112]. Several HuR targets encode proteins important for tumorigenesis. Finally, miR-125a-3p regulated DCT-induced apoptosis and DCT sensitivity through its target MTA1, a protein that plays a pivotal role in signal regulation by modifying the acetylation status of crucial genes [113]. Moreover, authors noticed that miR-125a-3p overexpressing cells exhibited a round shape that rendered these cells more similar to epithelial cells rather than mesenchymal, hypothesizing an EMT.

3.2. Modification of drug efflux transporters.

One of the more consolidated mechanism of DCT resistance is drug efflux due to the upregulation of the ABC transporter (paragraph 2.2). Some miRNAs modulated DCT resistance by

regulating the ABC transporters expression, as already seen for miR-204 that also acts by targeting ABCB1 (MDR1) expression (paragraph 3.1). Another more recent study identified miR-204-5p (this is the current ID of miR-204 according to the latest miRbase release -22.1, October 2018-, see Table 1) as a regulator of ABC transporters [114]. In particular, the authors discovered that lncRNA NEAT1, that is upregulated in DCT^R PCa cells and tissues, induces DCT resistance by sponging both miR-204-5p and miR-34a-5p which in turn release their common target ACSL4. ACSL4 is involved in drug resistance by distinct pathways. In this work the authors demonstrated that its upregulation due to NEAT1/miRNAs alteration in DCT^R PCa cells enhanced ABCG2 (MRX) and ABCC4 (MRP4) expression and also invasion and migration. In a similar work, Ma et al. demonstrated that miR-34a-5p is involved in another circuit that affects DCT resistance through the regulation of the ABC transporters together with lncRNA DANCR and JAGI [115]. Specifically, DANCR, by sponging miR-34a-5p, derepresses JAGI that in turn promotes DCT resistance by inducing the increase of ABCB1 (MDR1) and ABCC4 (MRP4) expression and, also in this case, invasion and migration. Of note, DANCR and JAGI are upregulated while miR-34a-5p is downregulated in DCT-resistant (DCT^R) PCa tissues.

3.3. Antioxidant response activation.

A recent work demonstrated the involvement of a miRNA (miR-193a-5p) in the regulation of the antioxidant responses induced by DCT treatment and in DCT resistance in PCa [116]. Indeed, miR-193a-5p mediated the heme oxygenase-1 (HO-1) induction after DCT treatment. HO-1 is a cytoprotective enzyme with antioxidant properties [117]. During oxidative stress caused by chemotherapeutic agents, cancer cells induce antioxidant factors and reduce apoptosis to protect against the oxidative injury. Authors demonstrated that the DCT-induced miR-193a-5p inhibits BACH2, a repressor of HO-1. They also showed that ectopic expression of miR-193-5p reduced the apoptosis induced by oxidative stress (H_2O_2 treatment). Indeed, they demonstrated that the HO-1 upregulation counteracts in part the DCT-induced apoptosis by inducing BCL2 upregulation and

BAX downregulation. Finally, they also validated the axis in xenograft model, in which the injected PCa cells depleted of miR-193a-5p were more sensitive to DCT toxicity than the injected control cells.

3.4. EMT activation.

As already mentioned, cancers cells undergoing EMT exhibit increased DCT resistance (paragraph 2.2). Indeed, we previously reported that two miRNAs that affected DCT sensitivity by modulating DCT-induced apoptosis also act probably by inducing EMT (miR-125a-3p) or regulating ZEB1 (miR-204) an important EMT transcription factor (paragraph 3.1). Puhr et al. demonstrated that two members of the miR-200 family (miR-200c and miR-205), which are known ZEB1/2 direct inhibitors, were downregulated in DCT^R PCa cells that underwent EMT (proved by the activation of EMT markers (including ZEB1/2) and by the increase of invasive/migratory potential) [118]. Authors also demonstrated that the miRNAs overexpression caused ZEB1/2 downregulation and the consequent E-cadherin upregulation. In another work, Zhang et al. demonstrated that ZEB1 expression was also regulated by miR-27b and miR-34a (this is the previous ID of miR-34a-5p according to the latest miRbase release -22.1, October 2018-, see Table 1) [119]. In particular, the overexpression of the two miRNAs in DCT^R PCa cells in which they are downregulated, increases the DCT sensitivity possibly by inhibiting EMT through ZEB1 direct inhibition and the consequent E-cadherin upregulation and vimentin downregulation. Furthermore, DCT^R PCa cells overexpressing miR-27b/-34a became more sensitive to DCT toxicity also in a xenograft model.

3.5. Cancer stem cells.

Increasing evidence indicates that the presence/formation of a subpopulation of cells within the tumor/tumor microenvironment with stemness characteristics (cancer stem cells, CSC) impaired drug efficacy, including DCT in PCa (paragraph 2.2). miRNAs could play a role in this phenomenon as shown by Qui et al. who demonstrated that DCT^R PCa cells are characterized by the enrichment

of cells with stemness characteristics [120]. In addition, these cells showed a strong EZH2 upregulation that was fundamental for the formation of CSC population in DCT^R PCa cells. Indeed, EZH2 inhibition decreases the number of CSC cells restoring DCT sensitivity. The authors showed that EZH2 is putatively targeted by miR-101-3p/-138-5p (EZH2 has been validated as miR-138-5p target by others). The two miRNAs not only are downregulated in DCT^R PCa cells, but their overexpression induces EZH2 inhibition and restores cells sensitivity to DCT, suggesting that they play a role in CSC formation/DCT resistance by regulating EZH2. It is of note that the EZH2-dependent epigenetic regulation might also be involved in miR-205/-31 DCT resistance (paragraph 3.1), even though in this case authors hypothesized an activating role of EZH2 on stem cell markers expression, thus excluding a PRC2 complex-dependent activity.

3.6. Others

Finally, also miR-200b [121] and miR-328 [122] affected DCT sensitivity of PCa cells. miR-200b regulates (directly or indirectly) BMI-1 expression and both miR-200b overexpression or BMI-1 silencing increase DCT sensitivity of PCa cells. As previously described (paragraph 2.2), BMI-1 is involved in DCT resistance by activating the antioxidant defense allowing PCa cells to survive the treatment [50]. Thus, it is possible that miR-200b may act on this mechanism of DCT resistance through BMI-1, even though other mechanisms cannot be excluded (e.g. EMT induction). In the same way, miR-328 overexpression increases DCT sensitivity as well as its target (PAK6) silencing. PAK6 has been already associated to DCT-resistance [123] and authors hypothesized that the mechanism could be ascribed to cytoskeleton inhibition, given that PAK6 signaling play an important role in cytoskeleton remodeling [124].

4. Clinical implications and concluding remarks

miRNAs play a relevant role in the regulation of the expression of coding/non coding genes that are fundamental for the development of DCT resistance in PCa. Considering the existing literature, miRNAs are involved in almost all the known mechanisms of DCT resistance. The majority of the miRNAs discovered as DCT-resistance regulators/modulators in PCa and hence object of this review (DCT-miRNAs) are involved in the fundamental pathways at the basis of "cell survival", in particular "apoptosis avoidance". As a single miRNA can regulate hundreds of genes, it is conceivable that the same miRNA can modulate DCT resistance by acting on multiple pathways. Indeed, several DCT-miRNAs affect more than one biological process associated to DCT-resistance (e.g. miR-204-5p, miR-34a-5p, etc.). For this characteristic, miRNAs represent potentially strong regulators of drug resistance pathways. This concept is supported by a conspicuous number of reports, especially in PCa. Indeed, miRNAs play a role in antiandrogen [125], cisplatin [126] and paclitaxel [127, 128] resistance. Moreover, miRNAs, modulate radiosensitivity of PCa cells by regulating mitochondrial antioxidant enzyme [129], hypoxia-induced autophagy [130], EMT [131] and cyclin D1-E1/pRB/E2F1 pathway [132].

Given the proven relevance of miRNAs in drug resistance regulation, the DCT-miRNAs could represent ideal therapeutic targets. Since DCT, in combination with second generation hormone therapy, is still the only therapeutic choice for metastatic CRPC (mCRPC), new therapeutic approaches based on DCT-miRNAs modulation could be attractive to overcome DCT resistance and/or to increase the current therapy efficacy when used in combination. The silencing of a miRNA whose overexpression increases drug resistance or the replacement of a miRNA whose downregulation decreases drug sensitivity could restore the sensitivity of cancer cells to a specific treatment. The miRNA overexpression is obtained using synthetic miRNA mimics, i.e. double-stranded small RNA molecules that match the corresponding miRNA sequences. On the hand, the miRNA silencing is achieved using antimiRs, single strand RNA molecules whose sequences are complementary to the corresponding miRNA and block its function by strongly binding to it. Several strategies have been developed to efficiently deliver the therapeutic miRNA/antimiRNA molecules

to the target cells in vivo, including chemical modifications to increase their stability or the use of viral or non-viral (nanoparticles) vectors (for review see [133, 134]). In particular, nanoparticles seem to be promising as they have several advantages, such as systemic stability and efficient delivery [135, 136]. Intriguingly, two different miRNA-based nanoparticles have been developed to increase the DCT cytotoxicity in PCa using DCT-miRNAs. Nagesh et al. [137] demonstrated that magnetic nanoparticles that bind miR-205 sensitized PCa cells to DCT. Furthermore, pH and glutathione sensitive nanocarriers for co-delivery of DCT and rubone (a miR-34 activator) efficiently increase DCT cytotoxicity in DCT resistant PCa cells *in vitro*, in 3D spheroid model and in xenograft model [138]. The possibility to develop nanoparticles carrying more than one compounds is particularly interesting when a therapy in combination with DCT is considered.

Another aspect is that the identification of the gene networks regulated by miRNAs related to drug resistance could allow the discovery of multiple potentially targetable genes/pathways. A series of pre-clinical/clinical studies regarding compounds that target the genes and/or pathways regulated by DCT-miRNAs corroborate the previous statement. E.g. the ABCC1 transporter inhibition obtained using its inhibitors reversan and MK571 sensitized PCa cells to DCT [139]; the HDAC inhibitor mocetinostat interfered with ZEB1 expression and restored the DCT chemosensitivity in DCT resistant PCa cells partially reversing the EMT phenotype [140]; the BCL-W inhibitors ABT-263/ABT-737 significantly increased the antitumor effect of DCT on DCT PCa resistant cells [33]; custirsen, an antisense oligonucleotide that inhibit the production of clusterin, showed promising results in a randomized phase III trials in combination with cabazitaxel and prednisone in mCRPC PCa patients that progress after DCT therapy [141]. In addition, several existing compounds targeting DCT-miRNAs targets could be evaluated as possible treatment to potentiate DCT cytotoxicity. The inhibition of SIRT1 (one of the miR-204 targets) could restore DCT sensitivity by enhancing DCT-induced apoptosis. The SIRT1 inhibitors nicotinamide and sirtinol have been shown to decrease PCa cells growth and viability [142]. Similarly, EZH2 (the miR-138-5p direct target) inhibition could increase DCT sensitivity by decreasing the CSC subpopulation. The EZH2 inhibition by CPI-1205

or PF-06821497 has been evaluated in combination with other standard treatments in mCRPC and CRPC patients respectively [143]. Moreover, EZH2 inhibition by GSK126 overcomes enzalutamide resistance both in vitro and in xenograft PCa models [144]. Finally, trametinib, a MEK1/2 inhibitor approved in melanoma treatment, has been shown to elicit a strong clinical response in mCRPC patients who failed multiple prior treatments [145]. MAPK/ERK signaling pathway is often activated in DCT resistance associated to DCT-miRNAs that affect "survival pathways/apoptosis escape". It has to be considered that DCT resistance, as well as others drug resistances, is a multifactorial phenomenon that could depend on the predominance of a specific resistant pathway or by the combination of more than one pathway. In these cases, identifying the prevalent pathway/s responsible for DCT resistance could help in selecting the most efficacious compound to be used in combination with post-DCT standard treatment for building personalized therapy. It is also true that different resistant mechanisms share similar pathways (e.g. EMT-CSC, EMT-CSC-survival/apoptosis avoidance pathways, etc.), and, as a consequence, some genes/pathways could represent key hub regulators of DCT resistance and as such they could be the ideal therapeutic targets to use in combination with DCT to limit the risk of resistance.

For all these considerations, the effort of this review was not only to describe the miRNAs involved in docetaxel resistance, but also to classify them, according to regulated target/s and/or affected biological process/es, in a specific pathway/s of docetaxel resistance. It should be also emphasized that improving the knowledge of the molecular networks (composed by coding and non-coding RNA) that contribute to DCT resistance in PCa could also be important in deciphering the resistance mechanisms to other taxanes/treatments in PCa or in different tumor types. Indeed, several DCT-miRNAs also have a role in the resistance to other treatments in PCa. E.g. miR-34a attenuated paclitaxel resistance [146] by regulating the JAG1/NOTCH axis [147]; miR-145 [148] and miR-205 [149] enhanced radiation sensitivity by impairing, for miR-205, DNA damage repair through PKCε and ZEB1 inhibition; miR-181 [150] and miR-205 [151] decreased and enhanced cisplatin

cytotoxicity respectively by inhibiting BAX (miR-181) and by impairing the autophagic flux (miR-205).

Finally, related to the fact that DCT-miRNAs expression levels change in resistant cells/tissues, they could represent useful biomarkers of DCT resistance. Indeed, some of the DCT-miRNAs were measured in human PCa specimens and their potential clinical relevance were demonstrated. In particular, the expression of miR-125a-3p [113], miR-34a-5p [115] and miR-204 [102] significantly decreased in DCT-resistant compared to DCT-sensitive PCa tissues, making them ideal candidate predictive biomarkers. It has to be considered that a biomarker able to detect the early appearance of DCT resistance could greatly help clinicians to select the most efficacious therapy sequence. From this point of view, circulating miRNAs (c-miRNAs) [152-154] represent ideal biomarkers given that they are easy detectable with minimally invasive procedures unlike tissue miRNAs. A few preliminary studies have explored c-miRNAs as DCT predictive biomarkers in PCa patients [155-158]. The increased serum level of miR-21 [155] and miR-210 [156] is potentially predictive of DCT resistance. Interestingly, in a work published in 2017, we demonstrated that miR-210-3p and miR-21-5p were also specifically released by DCT resistant PCa clones compared to parental cells [159]. Recently, Zedan et al. showed that miR-141 and miR-375 plasma levels may predict the progression in mCRPC patients treated with DCT and abiraterone [160].

In conclusion, the increasing knowledge of the molecular networks, including miRNA networks, at the basis of drug resistance mechanisms will be fundamental to drive research toward new therapeutic paradigms for the treatment of cancer type for which, at least at certain stage, current treatments are poorly effective.

Declaration of Competing Interest

The author declares no conflicts of interest

Acknowledgments

I would like to thank Dr. Marcella Simili, Dr. Letizia Pitto, Dr. Francesca Patella and Dr. Mike Minks for critical reading of the manuscript and Dr. Mike Minks for the revision and language editing of the manuscript. I also would like to thank the reviewers for their helpful comments towards improving the manuscript.

Table 1. miRNAs involved in DCT resistance in Prostate Cancer

miRNA paper ID[1]	miRNA current ID[2]	Biological process	Validated target/s	DCT resistance[3]	Reference
miR-143	miR-143-3p	Cell survival	IGF-1R*, IRS1*	decrease	[85]
			KRAS	decrease	[86]
miR-183	miR-183-5p	Cell survival/ apoptosis escape	SPRY2	increase	[87]
miR-21	miR-21-5p		PDCD4	increase	[89]
miR-205#	miR-205-5p	Apoptosis escape	BCL-W	decrease	[92, 93]
miR-31	miR-31-5p		E2F6	decrease	
miR-195	NI		Clusterin	decrease	[95]
miR-223-3p	-		FOXO3	increase	[96]
miR-323	miR-323a-3p		p73	increase	[97]
miR-4735-3p	-		MEKK1	increase	[98]
miR-375	NI		SEC23A*, YAP1*	increase	[99]
miR-217	NI		-	decrease	[100]
miR-181b-5p	-		-	decrease	
miR-181a	miR-181a-5p		-	increase	[101]
miR-204#	miR-204-5p	Apoptosis escape, EMT-TF, drug efflux	ZEB1	decrease	[102]
			SIRT1*	decrease	[105]
miR-129-5p	-	Apoptosis escape, cell survival, migration/invasion	CAMK2N1	increase	[106]
miR-138#	miR-138-5p	Apoptosis escape, cell spreading	KINDLIN-2	decrease	[107]
miR-145-5p	-	Apoptosis escape, migration/invasion	AKAP12	decrease	[110]
miR-125a-3p	-	Apoptosis escape, EMT	MTA1	decrease	[113]
miR-133b	-	Apoptosis escape, drug efflux	HuR	decrease	[111]
miR-204-5p#	-	Drug efflux, migration/invasion	ACSL4	decrease	[114]
miR-34a-5p#	-			decrease	
miR-34a-5p#	-		JAGI	decrease	[115]
miR-193a-5p	-	Antioxidant response	BACH2	increase	[116]
miR-200c	miR-200c-3p	EMT	ZEB1/2*	decrease	[118]
miR-205#	miR-205-5p			decrease	
miR-27b	miR-27b-3p		ZEB1	decrease	[119]
miR-34a#	miR-34a-5p			decrease	
miR-101-3p	-	Cancer stem cells	EZH2*	decrease	[120]
miR-138-5p#	-			decrease	
miR-328	NI	Others	PAK6	decrease	[122]
miR-200b	miR-200b-3p		-	decrease	[121]

[1]miRNAs ID indicated in the reference paper.
[2]miRNAs ID indicated in the latest miRbase release (22.1, 2018) if different from the reference paper. NI, not indicated in the latest miRbase release. In the manuscript the ID indicated in the reference paper was used.
[3]In this column miRNA that act increasing or decreasing DCT resistance in PCa were indicated.
#miRNAs involved in more than one mechanism of DCT resistance.
*miRNAs targets that have not been validated in the reference paper. EZH2 has been validated only as miR-138-5p target.

References

[1] F. Bray, J. Ferlay, I. Soerjomataram, R.L. Siegel, L.A. Torre, A. Jemal, Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J Clin 68(6) (2018) 394-424.

[2] G. Wang, D. Zhao, D.J. Spring, R.A. DePinho, Genetics and biology of prostate cancer, Genes Dev 32(17-18) (2018) 1105-1140.

[3] D.I. Quinn, H.M. Sandler, L.G. Horvath, A. Goldkorn, J.A. Eastham, The evolution of chemotherapy for the treatment of prostate cancer, Ann Oncol 28(11) (2017) 2658-2669.

[4] R. Nader, J. El Amm, J.B. Aragon-Ching, Role of chemotherapy in prostate cancer, Asian J Androl 20(3) (2018) 221-229.

[5] S. Sumanasuriya, J. De Bono, Treatment of Advanced Prostate Cancer-A Review of Current Therapies and Future Promise, Cold Spring Harb Perspect Med 8(6) (2018).

[6] J.S. de Bono, C.J. Logothetis, A. Molina, K. Fizazi, S. North, L. Chu, K.N. Chi, R.J. Jones, O.B. Goodman, Jr., F. Saad, J.N. Staffurth, P. Mainwaring, S. Harland, T.W. Flaig, T.E. Hutson, T. Cheng, H. Patterson, J.D. Hainsworth, C.J. Ryan, C.N. Sternberg, S.L. Ellard, A. Flechon, M. Saleh, M. Scholz, E. Efstathiou, A. Zivi, D. Bianchini, Y. Loriot, N. Chieffo, T. Kheoh, C.M. Haqq, H.I. Scher, C.-A.-. Investigators, Abiraterone and increased survival in metastatic prostate cancer, N Engl J Med 364(21) (2011) 1995-2005.

[7] H.I. Scher, K. Fizazi, F. Saad, M.E. Taplin, C.N. Sternberg, K. Miller, R. de Wit, P. Mulders, K.N. Chi, N.D. Shore, A.J. Armstrong, T.W. Flaig, A. Flechon, P. Mainwaring, M. Fleming, J.D. Hainsworth, M. Hirmand, B. Selby, L. Seely, J.S. de Bono, A. Investigators, Increased survival with enzalutamide in prostate cancer after chemotherapy, N Engl J Med 367(13) (2012) 1187-97.

[8] T.M. Beer, B. Tombal, Enzalutamide in metastatic prostate cancer before chemotherapy, N Engl J Med 371(18) (2014) 1755-6.

[9] E. Kopczynska, Role of microRNAs in the resistance of prostate cancer to docetaxel and paclitaxel, Contemp Oncol (Pozn) 19(6) (2015) 423-7.

[10] F. Li, R.I. Mahato, MicroRNAs and drug resistance in prostate cancers, Mol Pharm 11(8) (2014) 2539-52.

[11] A. Razdan, P. de Souza, T.L. Roberts, Role of MicroRNAs in Treatment Response in Prostate Cancer, Curr Cancer Drug Targets 18(10) (2018) 929-944.

[12] M.A. Jordan, L. Wilson, Microtubules as a target for anticancer drugs, Nat Rev Cancer 4(4) (2004) 253-65.

[13] R.S. Herbst, F.R. Khuri, Mode of action of docetaxel - a basis for combination with novel anticancer agents, Cancer Treat Rev 29(5) (2003) 407-15.

[14] G. Kramer, S. Schwarz, M. Hagg, A.M. Havelka, S. Linder, Docetaxel induces apoptosis in hormone refractory prostate carcinomas during multiple treatment cycles, Br J Cancer 94(11) (2006) 1592-8.

[15] F. Fabbri, D. Amadori, S. Carloni, G. Brigliadori, A. Tesei, P. Ulivi, M. Rosetti, I. Vannini, C. Arienti, W. Zoli, R. Silvestrini, Mitotic catastrophe and apoptosis induced by docetaxel in hormone-refractory prostate cancer cells, J Cell Physiol 217(2) (2008) 494-501.

[16] J. Mang, K. Merkle, M. Heller, J. Schuler, Y. Tolstov, J. Li, M. Hohenfellner, S. Duensing, Molecular complexity of taxane-induced cytotoxicity in prostate cancer cells, Urol Oncol 35(1) (2017) 32 e9-32 e16.

[17] M.S. Darshan, M.S. Loftus, M. Thadani-Mulero, B.P. Levy, D. Escuin, X.K. Zhou, A. Gjyrezi, C. Chanel-Vos, R. Shen, S.T. Tagawa, N.H. Bander, D.M. Nanus, P. Giannakakou, Taxane-induced blockade to nuclear accumulation of the androgen receptor predicts clinical responses in metastatic prostate cancer, Cancer Res 71(18) (2011) 6019-29.

[18] M. Thadani-Mulero, D.M. Nanus, P. Giannakakou, Androgen receptor on the move: boarding the microtubule expressway to the nucleus, Cancer Res 72(18) (2012) 4611-5.

[19] G. Galletti, B.I. Leach, L. Lam, S.T. Tagawa, Mechanisms of resistance to systemic therapy in metastatic castration-resistant prostate cancer, Cancer Treat Rev 57 (2017) 16-27.
[20] S. Giacinti, G. Poti, M. Roberto, S. Macrini, M. Bassanelli, D.I.P. F, A.M. Aschelter, A. Ceribelli, E.M. Ruggeri, P. Marchetti, Molecular Basis of Drug Resistance and Insights for New Treatment Approaches in mCRPC, Anticancer Res 38(11) (2018) 6029-6039.
[21] G. Ploussard, S. Terry, P. Maille, Y. Allory, N. Sirab, L. Kheuang, P. Soyeux, N. Nicolaiew, E. Coppolani, B. Paule, L. Salomon, S. Culine, R. Buttyan, F. Vacherot, A. de la Taille, Class III beta-tubulin expression predicts prostate tumor aggressiveness and patient response to docetaxel-based chemotherapy, Cancer Res 70(22) (2010) 9253-64.
[22] S. Terry, G. Ploussard, Y. Allory, N. Nicolaiew, F. Boissiere-Michot, P. Maille, L. Kheuang, E. Coppolani, A. Ali, F. Bibeau, S. Culine, R. Buttyan, A. de la Taille, F. Vacherot, Increased expression of class III beta-tubulin in castration-resistant human prostate cancer, Br J Cancer 101(6) (2009) 951-6.
[23] T. Hara, K. Ushio, M. Nishiwaki, J. Kouno, H. Araki, Y. Hikichi, M. Hattori, Y. Imai, M. Yamaoka, A mutation in beta-tubulin and a sustained dependence on androgen receptor signalling in a newly established docetaxel-resistant prostate cancer cell line, Cell Biol Int 34(2) (2010) 177-84.
[24] J. Yang, Y. Yu, W. Liu, Z. Li, Z. Wei, R. Jiang, Microtubule-associated protein tau is associated with the resistance to docetaxel in prostate cancer cell lines, Res Rep Urol 9 (2017) 71-77.
[25] M.M. Gottesman, T. Fojo, S.E. Bates, Multidrug resistance in cancer: role of ATP-dependent transporters, Nat Rev Cancer 2(1) (2002) 48-58.
[26] D.E. Oprea-Lager, I.V. Bijnsdorp, V.A.N.M. RJ, V.D.E. AJ, O.S. Hoekstra, A.A. Geldof, ABCC4 Decreases docetaxel and not cabazitaxel efficacy in prostate cancer cells in vitro, Anticancer Res 33(2) (2013) 387-91.
[27] Y. Zhu, C. Liu, N. Nadiminty, W. Lou, R. Tummala, C.P. Evans, A.C. Gao, Inhibition of ABCB1 expression overcomes acquired docetaxel resistance in prostate cancer, Mol Cancer Ther 12(9) (2013) 1829-36.
[28] C. Liu, Z. Li, L. Bi, K. Li, B. Zhou, C. Xu, J. Huang, K. Xu, NOTCH1 signaling promotes chemoresistance via regulating ABCC1 expression in prostate cancer stem cells, Mol Cell Biochem 393(1-2) (2014) 265-70.
[29] C.A. Martins, G.D.G. Rocha, C.R. Gattass, C.M. Takiya, Pomolic acid exhibits anticancer potential against a docetaxelresistant PC3 prostate cell line, Oncol Rep 42(1) (2019) 328-338.
[30] L. Magadoux, N. Isambert, S. Plenchette, J.F. Jeannin, V. Laurens, Emerging targets to monitor and overcome docetaxel resistance in castration resistant prostate cancer (review), Int J Oncol 45(3) (2014) 919-28.
[31] T. Chandrasekar, J.C. Yang, A.C. Gao, C.P. Evans, Mechanisms of resistance in castration-resistant prostate cancer (CRPC), Transl Androl Urol 4(3) (2015) 365-80.
[32] R. Parrondo, A. de Las Pozas, T. Reiner, C. Perez-Stable, ABT-737, a small molecule Bcl-2/Bcl-xL antagonist, increases antimitotic-mediated apoptosis in human prostate cancer cells, PeerJ 1 (2013) e144.
[33] H. Tamaki, N. Harashima, M. Hiraki, N. Arichi, N. Nishimura, H. Shiina, K. Naora, M. Harada, Bcl-2 family inhibition sensitizes human prostate cancer cells to docetaxel and promotes unexpected apoptosis under caspase-9 inhibition, Oncotarget 5(22) (2014) 11399-412.
[34] S.J. Hotte, Addressing taxane resistance in metastatic castration-resistant prostate cancer: a focus on chaperone proteins, Future Oncol 13(4) (2017) 369-379.
[35] J.Y. Djeu, S. Wei, Clusterin and chemoresistance, Adv Cancer Res 105 (2009) 77-92.
[36] B. Zhong, D.A. Sallman, D.L. Gilvary, D. Pernazza, E. Sahakian, D. Fritz, J.Q. Cheng, I. Trougakos, S. Wei, J.Y. Djeu, Induction of clusterin by AKT--role in cytoprotection against docetaxel in prostate tumor cells, Mol Cancer Ther 9(6) (2010) 1831-41.

[37] L.A. Muhammad, F. Saad, The role of clusterin in prostate cancer: treatment resistance and potential as a therapeutic target, Expert Rev Anticancer Ther 15(9) (2015) 1049-61.
[38] K. Tantivejkul, R.D. Loberg, S.C. Mawocha, L.L. Day, L.S. John, B.A. Pienta, M.A. Rubin, K.J. Pienta, PAR1-mediated NFkappaB activation promotes survival of prostate cancer cells through a Bcl-xL-dependent mechanism, J Cell Biochem 96(3) (2005) 641-52.
[39] P. Toren, A. Zoubeidi, Targeting the PI3K/Akt pathway in prostate cancer: challenges and opportunities (review), Int J Oncol 45(5) (2014) 1793-801.
[40] S.K. Singh, T. Apata, J.B. Gordetsky, R. Singh, Docetaxel Combined with Thymoquinone Induces Apoptosis in Prostate Cancer Cells via Inhibition of the PI3K/AKT Signaling Pathway, Cancers (Basel) 11(9) (2019).
[41] X. Lu, F. Yang, D. Chen, Q. Zhao, D. Chen, H. Ping, N. Xing, Quercetin reverses docetaxel resistance in prostate cancer via androgen receptor and PI3K/Akt signaling pathways, Int J Biol Sci 16(7) (2020) 1121-1134.
[42] S. Zelivianski, M. Spellman, M. Kellerman, V. Kakitelashvilli, X.W. Zhou, E. Lugo, M.S. Lee, R. Taylor, T.L. Davis, R. Hauke, M.F. Lin, ERK inhibitor PD98059 enhances docetaxel-induced apoptosis of androgen-independent human prostate cancer cells, Int J Cancer 107(3) (2003) 478-85.
[43] Z. Liu, G. Zhu, R.H. Getzenberg, R.W. Veltri, The Upregulation of PI3K/Akt and MAP Kinase Pathways is Associated with Resistance of Microtubule-Targeting Drugs in Prostate Cancer, J Cell Biochem 116(7) (2015) 1341-9.
[44] S.J. Vidal, V. Rodriguez-Bravo, S.A. Quinn, R. Rodriguez-Barrueco, A. Lujambio, E. Williams, X. Sun, J. de la Iglesia-Vicente, A. Lee, B. Readhead, X. Chen, M. Galsky, B. Esteve, D.P. Petrylak, J.T. Dudley, R. Rabadan, J.M. Silva, Y. Hoshida, S.W. Lowe, C. Cordon-Cardo, J. Domingo-Domenech, A targetable GATA2-IGF2 axis confers aggressiveness in lethal prostate cancer, Cancer Cell 27(2) (2015) 223-39.
[45] S.R. Plymate, R.S. Bhatt, S.P. Balk, Taxane resistance in prostate cancer mediated by AR-independent GATA2 regulation of IGF2, Cancer Cell 27(2) (2015) 158-9.
[46] B. Seruga, A. Ocana, I.F. Tannock, Drug resistance in metastatic castration-resistant prostate cancer, Nat Rev Clin Oncol 8(1) (2011) 12-23.
[47] M. Thadani-Mulero, L. Portella, S. Sun, M. Sung, A. Matov, R.L. Vessella, E. Corey, D.M. Nanus, S.R. Plymate, P. Giannakakou, Androgen receptor splice variants determine taxane sensitivity in prostate cancer, Cancer Res 74(8) (2014) 2270-2282.
[48] G. Zhang, X. Liu, J. Li, E. Ledet, X. Alvarez, Y. Qi, X. Fu, O. Sartor, Y. Dong, H. Zhang, Androgen receptor splice variants circumvent AR blockade by microtubule-targeting agents, Oncotarget 6(27) (2015) 23358-71.
[49] E.S. Antonarakis, C. Lu, B. Luber, H. Wang, Y. Chen, M. Nakazawa, R. Nadal, C.J. Paller, S.R. Denmeade, M.A. Carducci, M.A. Eisenberger, J. Luo, Androgen Receptor Splice Variant 7 and Efficacy of Taxane Chemotherapy in Patients With Metastatic Castration-Resistant Prostate Cancer, JAMA Oncol 1(5) (2015) 582-91.
[50] F. Crea, M.A. Duhagon Serrat, E.M. Hurt, S.B. Thomas, R. Danesi, W.L. Farrar, BMI1 silencing enhances docetaxel activity and impairs antioxidant response in prostate cancer, Int J Cancer 128(8) (2011) 1946-54.
[51] T. Rabi, A. Bishayee, d -Limonene sensitizes docetaxel-induced cytotoxicity in human prostate cancer cells: Generation of reactive oxygen species and induction of apoptosis, J Carcinog 8 (2009) 9.
[52] G. Varbiro, B. Veres, F. Gallyas, Jr., B. Sumegi, Direct effect of Taxol on free radical formation and mitochondrial permeability transition, Free Radic Biol Med 31(4) (2001) 548-58.
[53] S. Datta, D. Choudhury, A. Das, D. Das Mukherjee, N. Das, S.S. Roy, G. Chakrabarti, Paclitaxel resistance development is associated with biphasic changes in reactive oxygen species, mitochondrial membrane potential and autophagy with elevated energy production

capacity in lung cancer cells: A chronological study, Tumour Biol 39(2) (2017) 1010428317694314.
[54] D. Zhang, Y. Cui, L. Niu, X. Xu, K. Tian, C.Y. Young, H. Lou, H. Yuan, Regulation of SOD2 and beta-arrestin1 by interleukin-6 contributes to the increase of IGF-1R expression in docetaxel resistant prostate cancer cells, Eur J Cell Biol 93(7) (2014) 289-98.
[55] Y. Tang, B. Parmakhtiar, A.R. Simoneau, J. Xie, J. Fruehauf, M. Lilly, X. Zi, Lycopene enhances docetaxel's effect in castration-resistant prostate cancer associated with insulin-like growth factor I receptor levels, Neoplasia 13(2) (2011) 108-19.
[56] E.S. Antonarakis, A.J. Armstrong, Evolving standards in the treatment of docetaxel-refractory castration-resistant prostate cancer, Prostate Cancer Prostatic Dis 14(3) (2011) 192-205.
[57] P. Pucci, P. Rescigno, S. Sumanasuriya, J. de Bono, F. Crea, Hypoxia and Noncoding RNAs in Taxane Resistance, Trends Pharmacol Sci 39(8) (2018) 695-709.
[58] J. van Staalduinen, D. Baker, P. Ten Dijke, H. van Dam, Epithelial-mesenchymal-transition-inducing transcription factors: new targets for tackling chemoresistance in cancer?, Oncogene 37(48) (2018) 6195-6211.
[59] H. Manoochehri Khoshinani, S. Afshar, R. Najafi, Hypoxia: A Double-Edged Sword in Cancer Therapy, Cancer Invest 34(10) (2016) 536-545.
[60] X. Jing, F. Yang, C. Shao, K. Wei, M. Xie, H. Shen, Y. Shu, Role of hypoxia in cancer therapy by regulating the tumor microenvironment, Mol Cancer 18(1) (2019) 157.
[61] J.M. Farrow, J.C. Yang, C.P. Evans, Autophagy as a modulator and target in prostate cancer, Nat Rev Urol 11(9) (2014) 508-16.
[62] F. Hu, Y. Zhao, Y. Yu, J.M. Fang, R. Cui, Z.Q. Liu, X.L. Guo, Q. Xu, Docetaxel-mediated autophagy promotes chemoresistance in castration-resistant prostate cancer cells by inhibiting STAT3, Cancer Lett 416 (2018) 24-30.
[63] J. Zeng, W. Liu, Y.Z. Fan, D.L. He, L. Li, PrLZ increases prostate cancer docetaxel resistance by inhibiting LKB1/AMPK-mediated autophagy, Theranostics 8(1) (2018) 109-123.
[64] Q. Wang, W.Y. He, Y.Z. Zeng, A. Hossain, X. Gou, Inhibiting autophagy overcomes docetaxel resistance in castration-resistant prostate cancer cells, Int Urol Nephrol 50(4) (2018) 675-686.
[65] J. Jia, H.B. Zhang, Q. Shi, C. Yang, J.B. Ma, B. Jin, X. Wang, D. He, P. Guo, KLF5 downregulation desensitizes castration-resistant prostate cancer cells to docetaxel by increasing BECN1 expression and inducing cell autophagy, Theranostics 9(19) (2019) 5464-5477.
[66] J.Z. Lin, W.W. Wang, T.T. Hu, G.Y. Zhu, L.N. Li, C.Y. Zhang, Z. Xu, H.B. Yu, H.F. Wu, J.G. Zhu, FOXM1 contributes to docetaxel resistance in castration-resistant prostate cancer by inducing AMPK/mTOR-mediated autophagy, Cancer Lett 469 (2020) 481-489.
[67] S. Luo, L. Shao, Z. Chen, D. Hu, L. Jiang, W. Tang, NPRL2 promotes docetaxel chemoresistance in castration resistant prostate cancer cells by regulating autophagy through the mTOR pathway, Exp Cell Res 390(2) (2020) 111981.
[68] M. Singh, N. Yelle, C. Venugopal, S.K. Singh, EMT: Mechanisms and therapeutic implications, Pharmacol Ther 182 (2018) 80-94.
[69] S.A. Mani, W. Guo, M.J. Liao, E.N. Eaton, A. Ayyanan, A.Y. Zhou, M. Brooks, F. Reinhard, C.C. Zhang, M. Shipitsin, L.L. Campbell, K. Polyak, C. Brisken, J. Yang, R.A. Weinberg, The epithelial-mesenchymal transition generates cells with properties of stem cells, Cell 133(4) (2008) 704-15.
[70] T. Shibue, R.A. Weinberg, EMT, CSCs, and drug resistance: the mechanistic link and clinical implications, Nat Rev Clin Oncol 14(10) (2017) 611-629.
[71] S. Figiel, C. Vasseur, F. Bruyere, F. Rozet, K. Maheo, G. Fromont, Clinical significance of epithelial-mesenchymal transition markers in prostate cancer, Hum Pathol 61 (2017) 26-32.
[72] K.A. Cheaito, H.F. Bahmad, O. Hadadeh, E. Saleh, C. Dagher, M.S. Hammoud, M. Shahait, Z.A. Mrad, S. Nassif, A. Tawil, M. Bulbul, R. Khauli, W. Wazzan, R. Nasr, A. Shamseddine,

S. Temraz, M.E. El-Sabban, A. El-Hajj, D. Mukherji, W. Abou-Kheir, EMT Markers in Locally-Advanced Prostate Cancer: Predicting Recurrence?, Front Oncol 9 (2019) 131.
[73] M. Marin-Aguilera, J. Codony-Servat, O. Reig, J.J. Lozano, P.L. Fernandez, M.V. Pereira, N. Jimenez, M. Donovan, P. Puig, L. Mengual, R. Bermudo, A. Font, E. Gallardo, M.J. Ribal, A. Alcaraz, P. Gascon, B. Mellado, Epithelial-to-mesenchymal transition mediates docetaxel resistance and high risk of relapse in prostate cancer, Mol Cancer Ther 13(5) (2014) 1270-84.
[74] J. Caramel, M. Ligier, A. Puisieux, Pleiotropic Roles for ZEB1 in Cancer, Cancer Res 78(1) (2018) 30-35.
[75] K. Hanrahan, A. O'Neill, M. Prencipe, J. Bugler, L. Murphy, A. Fabre, M. Puhr, Z. Culig, K. Murphy, R.W. Watson, The role of epithelial-mesenchymal transition drivers ZEB1 and ZEB2 in mediating docetaxel-resistant prostate cancer, Mol Oncol 11(3) (2017) 251-265.
[76] O. Orellana-Serradell, D. Herrera, E.A. Castellon, H.R. Contreras, The transcription factor ZEB1 promotes chemoresistance in prostate cancer cell lines, Asian J Androl 21(5) (2019) 460-467.
[77] E. Batlle, H. Clevers, Cancer stem cells revisited, Nat Med 23(10) (2017) 1124-1134.
[78] M. Prieto-Vila, R.U. Takahashi, W. Usuba, I. Kohama, T. Ochiya, Drug Resistance Driven by Cancer Stem Cells and Their Niche, Int J Mol Sci 18(12) (2017).
[79] C.J. Lai, C.Y. Lin, W.Y. Liao, T.C. Hour, H.D. Wang, C.P. Chuu, CD44 Promotes Migration and Invasion of Docetaxel-Resistant Prostate Cancer Cells Likely via Induction of Hippo-Yap Signaling, Cells 8(4) (2019).
[80] S. Talukdar, S.K. Das, A.K. Pradhan, L. Emdad, J.J. Windle, D. Sarkar, P.B. Fisher, MDA-9/Syntenin (SDCBP) Is a Critical Regulator of Chemoresistance, Survival and Stemness in Prostate Cancer Stem Cells, Cancers (Basel) 12(1) (2019).
[81] S.U. Luk, W.N. Yap, Y.T. Chiu, D.T. Lee, S. Ma, T.K. Lee, R.S. Vasireddy, Y.C. Wong, Y.P. Ching, C. Nelson, Y.L. Yap, M.T. Ling, Gamma-tocotrienol as an effective agent in targeting prostate cancer stem cell-like population, Int J Cancer 128(9) (2011) 2182-91.
[82] M. Gruber, F. Handle, Z. Culig, The stem cell inhibitor salinomycin decreases colony formation potential and tumor-initiating population in docetaxel-sensitive and docetaxel-resistant prostate cancer cells, Prostate 80(3) (2020) 267-273.
[83] Y.Q. Liu, S.K. Wang, Q.Q. Xu, H.Q. Yuan, Y.X. Guo, Q. Wang, F. Kong, Z.M. Lin, D.Q. Sun, R.M. Wang, H.X. Lou, Acetyl-11-keto-beta-boswellic acid suppresses docetaxel-resistant prostate cancer cells in vitro and in vivo by blocking Akt and Stat3 signaling, thus suppressing chemoresistant stem cell-like properties, Acta Pharmacol Sin 40(5) (2019) 689-698.
[84] G. Canesin, V. Maggio, M. Palominos, A. Stiehm, H.R. Contreras, E.A. Castellon, J. Morote, R. Paciucci, N.J. Maitland, A. Bjartell, R. Hellsten, STAT3 inhibition with galiellalactone effectively targets the prostate cancer stem-like cell population, Sci Rep 10(1) (2020) 13958.
[85] X.B. Niu, G.B. Fu, L. Wang, X. Ge, W.T. Liu, Y.Y. Wen, H.R. Sun, L.Z. Liu, Z.J. Wang, B.H. Jiang, Insulin-like growth factor-I induces chemoresistence to docetaxel by inhibiting miR-143 in human prostate cancer, Oncotarget 8(63) (2017) 107157-107166.
[86] B. Xu, X. Niu, X. Zhang, J. Tao, D. Wu, Z. Wang, P. Li, W. Zhang, H. Wu, N. Feng, Z. Wang, L. Hua, X. Wang, miR-143 decreases prostate cancer cells proliferation and migration and enhances their sensitivity to docetaxel through suppression of KRAS, Mol Cell Biochem 350(1-2) (2011) 207-13.
[87] W. Gao, S. Lin, C. Cheng, A. Zhu, Y. Hu, Z. Shi, X. Zhang, Z. Hong, Long non-coding RNA CASC2 regulates Sprouty2 via functioning as a competing endogenous RNA for miR-183 to modulate the sensitivity of prostate cancer cells to docetaxel, Arch Biochem Biophys 665 (2019) 69-78.
[88] A.B. McKie, D.A. Douglas, S. Olijslagers, J. Graham, M.M. Omar, R. Heer, V.J. Gnanapragasam, C.N. Robson, H.Y. Leung, Epigenetic inactivation of the human sprouty2 (hSPRY2) homologue in prostate cancer, Oncogene 24(13) (2005) 2166-74.

[89] G.H. Shi, D.W. Ye, X.D. Yao, S.L. Zhang, B. Dai, H.L. Zhang, Y.J. Shen, Y. Zhu, Y.P. Zhu, W.J. Xiao, C.G. Ma, Involvement of microRNA-21 in mediating chemo-resistance to docetaxel in androgen-independent prostate cancer PC3 cells, Acta Pharmacol Sin 31(7) (2010) 867-73.
[90] B. Dong, Z. Shi, J. Wang, J. Wu, Z. Yang, K. Fang, IL-6 Inhibits the Targeted Modulation of PDCD4 by miR-21 in Prostate Cancer, PLoS One 10(8) (2015) e0134366.
[91] J. Domingo-Domenech, C. Oliva, A. Rovira, J. Codony-Servat, M. Bosch, X. Filella, C. Montagut, M. Tapia, C. Campas, L. Dang, M. Rolfe, J.S. Ross, P. Gascon, J. Albanell, B. Mellado, Interleukin 6, a nuclear factor-kappaB target, predicts resistance to docetaxel in hormone-independent prostate cancer and nuclear factor-kappaB inhibition by PS-1145 enhances docetaxel antitumor activity, Clin Cancer Res 12(18) (2006) 5578-86.
[92] N. Bhatnagar, X. Li, S.K. Padi, Q. Zhang, M.S. Tang, B. Guo, Downregulation of miR-205 and miR-31 confers resistance to chemotherapy-induced apoptosis in prostate cancer cells, Cell Death Dis 1 (2010) e105.
[93] Q. Zhang, S.K. Padi, D.J. Tindall, B. Guo, Polycomb protein EZH2 suppresses apoptosis by silencing the proapoptotic miR-31, Cell Death Dis 5 (2014) e1486.
[94] S. Varambally, S.M. Dhanasekaran, M. Zhou, T.R. Barrette, C. Kumar-Sinha, M.G. Sanda, D. Ghosh, K.J. Pienta, R.G. Sewalt, A.P. Otte, M.A. Rubin, A.M. Chinnaiyan, The polycomb group protein EZH2 is involved in progression of prostate cancer, Nature 419(6907) (2002) 624-9.
[95] X. Ma, L. Zou, X. Li, Z. Chen, Q. Lin, X. Wu, MicroRNA-195 regulates docetaxel resistance by targeting clusterin in prostate cancer, Biomed Pharmacother 99 (2018) 445-450.
[96] Q. Feng, P. He, Y. Wang, MicroRNA-223-3p regulates cell chemo-sensitivity by targeting FOXO3 in prostatic cancer, Gene 658 (2018) 152-158.
[97] Q. Gao, J. Zheng, microRNA-323 upregulation promotes prostate cancer growth and docetaxel resistance by repressing p73, Biomed Pharmacother 97 (2018) 528-534.
[98] W. Zhou, S. Huang, Q. Jiang, T. Yuan, Suppression of miR-4735-3p in androgen receptor-expressing prostate cancer cells increases cell death during chemotherapy, Am J Transl Res 9(8) (2017) 3714-3722.
[99] Y. Wang, R. Lieberman, J. Pan, Q. Zhang, M. Du, P. Zhang, M. Nevalainen, M. Kohli, N.K. Shenoy, H. Meng, M. You, L. Wang, miR-375 induces docetaxel resistance in prostate cancer by targeting SEC23A and YAP1, Mol Cancer 15(1) (2016) 70.
[100] H.M. Lin, I. Nikolic, J. Yang, L. Castillo, N. Deng, C.L. Chan, N.K. Yeung, E. Dodson, B. Elsworth, C. Spielman, B.Y. Lee, Z. Boyer, K.J. Simpson, R.J. Daly, L.G. Horvath, A. Swarbrick, MicroRNAs as potential therapeutics to enhance chemosensitivity in advanced prostate cancer, Sci Rep 8(1) (2018) 7820.
[101] C.M. Armstrong, C. Liu, W. Lou, A.P. Lombard, C.P. Evans, A.C. Gao, MicroRNA-181a promotes docetaxel resistance in prostate cancer cells, Prostate 77(9) (2017) 1020-1028.
[102] G. Wu, J. Wang, G. Chen, X. Zhao, microRNA-204 modulates chemosensitivity and apoptosis of prostate cancer cells by targeting zinc-finger E-box-binding homeobox 1 (ZEB1), Am J Transl Res 9(8) (2017) 3599-3610.
[103] L.Y. Chiu, I.L. Hsin, T.Y. Yang, W.W. Sung, J.Y. Chi, J.T. Chang, J.L. Ko, G.T. Sheu, The ERK-ZEB1 pathway mediates epithelial-mesenchymal transition in pemetrexed resistant lung cancer cells with suppression by vinca alkaloids, Oncogene 36(2) (2017) 242-253.
[104] Y. Gu, Y. Zhao, Y. Zhou, Y. Xie, P. Ju, Y. Long, J. Liu, D. Ni, F. Cao, Z. Lyu, Z. Mao, J. Hao, Y. Li, Q. Wan, Q. Kanyomse, Y. Liu, D. Ren, Y. Ning, X. Li, Q. Zhou, B. Li, Zeb1 Is a Potential Regulator of Six2 in the Proliferation, Apoptosis and Migration of Metanephric Mesenchyme Cells, Int J Mol Sci 17(8) (2016).
[105] X. Wang, B. Yang, B. Ma, The UCA1/miR-204/Sirt1 axis modulates docetaxel sensitivity of prostate cancer cells, Cancer Chemother Pharmacol 78(5) (2016) 1025-1031.

[106] C. Wu, C. Miao, Q. Tang, X. Zhou, P. Xi, P. Chang, L. Hua, H. Ni, MiR-129-5p promotes docetaxel resistance in prostate cancer by down-regulating CAMK2N1 expression, J Cell Mol Med 24(3) (2020) 2098-2108.
[107] K. Sossey-Alaoui, E.F. Plow, miR-138-Mediated Regulation of KINDLIN-2 Expression Modulates Sensitivity to Chemotherapeutics, Mol Cancer Res 14(2) (2016) 228-38.
[108] Y.X. Chen, Y. Wang, C.C. Fu, F. Diao, L.N. Song, Z.B. Li, R. Yang, J. Lu, Dexamethasone enhances cell resistance to chemotherapy by increasing adhesion to extracellular matrix in human ovarian cancer cells, Endocr Relat Cancer 17(1) (2010) 39-50.
[109] Y. Dong, O.L. Tan, D. Loessner, C. Stephens, C. Walpole, G.M. Boyle, P.G. Parsons, J.A. Clements, Kallikrein-related peptidase 7 promotes multicellular aggregation via the alpha(5)beta(1) integrin pathway and paclitaxel chemoresistance in serous epithelial ovarian carcinoma, Cancer Res 70(7) (2010) 2624-33.
[110] D. Xue, H. Lu, H.Y. Xu, C.X. Zhou, X.Z. He, Long noncoding RNA MALAT1 enhances the docetaxel resistance of prostate cancer cells via miR-145-5p-mediated regulation of AKAP12, J Cell Mol Med 22(6) (2018) 3223-3237.
[111] H. Liu, X. Song, J. Hou, Z. Zhao, J. Chang, Posttranscriptional Regulation of Human Antigen R by miR-133b Enhances Docetaxel Cytotoxicity Through the Inhibition of ATP-Binding Cassette Subfamily G Member 2 in Prostate Cancer Cells, DNA Cell Biol 37(3) (2018) 210-219.
[112] M. Wu, C.W.S. Tong, W. Yan, K.K.W. To, W.C.S. Cho, The RNA Binding Protein HuR: A Promising Drug Target for Anticancer Therapy, Curr Cancer Drug Targets 19(5) (2019) 382-399.
[113] J.Z. Liu, F.Y. Yin, C.Y. Yan, H. Wang, X.H. Luo, Regulation of Docetaxel Sensitivity in Prostate Cancer Cells by hsa-miR-125a-3p via Modulation of Metastasis-Associated Protein 1 Signaling, Urology 105 (2017) 208 e11-208 e17.
[114] X. Jiang, S. Guo, Y. Zhang, Y. Zhao, X. Li, Y. Jia, Y. Xu, B. Ma, LncRNA NEAT1 promotes docetaxel resistance in prostate cancer by regulating ACSL4 via sponging miR-34a-5p and miR-204-5p, Cell Signal 65 (2020) 109422.
[115] Y. Ma, B. Fan, Z. Ren, B. Liu, Y. Wang, Long noncoding RNA DANCR contributes to docetaxel resistance in prostate cancer through targeting the miR-34a-5p/JAG1 pathway, Onco Targets Ther 12 (2019) 5485-5497.
[116] Z. Yang, J.S. Chen, J.K. Wen, H.T. Gao, B. Zheng, C.B. Qu, K.L. Liu, M.L. Zhang, J.F. Gu, J.D. Li, Y.P. Zhang, W. Li, X.L. Wang, Y. Zhang, Silencing of miR-193a-5p increases the chemosensitivity of prostate cancer cells to docetaxel, J Exp Clin Cancer Res 36(1) (2017) 178.
[117] S.W. Ryter, J. Alam, A.M. Choi, Heme oxygenase-1/carbon monoxide: from basic science to therapeutic applications, Physiol Rev 86(2) (2006) 583-650.
[118] M. Puhr, J. Hoefer, G. Schafer, H.H. Erb, S.J. Oh, H. Klocker, I. Heidegger, H. Neuwirt, Z. Culig, 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 181(6) (2012) 2188-201.
[119] G. Zhang, X. Tian, Y. Li, Z. Wang, X. Li, C. Zhu, miR-27b and miR-34a enhance docetaxel sensitivity of prostate cancer cells through inhibiting epithelial-to-mesenchymal transition by targeting ZEB1, Biomed Pharmacother 97 (2018) 736-744.
[120] X. Qiu, W. Wang, B. Li, B. Cheng, K. Lin, J. Bai, H. Li, G. Yang, Targeting Ezh2 could overcome docetaxel resistance in prostate cancer cells, BMC Cancer 19(1) (2019) 27.
[121] J. Yu, Y. Lu, D. Cui, E. Li, Y. Zhu, Y. Zhao, F. Zhao, S. Xia, miR-200b suppresses cell proliferation, migration and enhances chemosensitivity in prostate cancer by regulating Bmi-1, Oncol Rep 31(2) (2014) 910-8.

[122] C. Liu, L. Zhang, Y. Huang, K. Lu, T. Tao, S. Chen, X. Zhang, H. Guan, M. Chen, B. Xu, MicroRNA328 directly targets p21activated protein kinase 6 inhibiting prostate cancer proliferation and enhancing docetaxel sensitivity, Mol Med Rep 12(5) (2015) 7389-95.
[123] X. Wen, X. Li, B. Liao, Y. Liu, J. Wu, X. Yuan, B. Ouyang, Q. Sun, X. Gao, Knockdown of p21-activated kinase 6 inhibits prostate cancer growth and enhances chemosensitivity to docetaxel, Urology 73(6) (2009) 1407-11.
[124] B. Dummler, K. Ohshiro, R. Kumar, J. Field, Pak protein kinases and their role in cancer, Cancer Metastasis Rev 28(1-2) (2009) 51-63.
[125] S. Rezaei, M. Mahjoubin Tehran, A. Sahebkar, A. Jalili, S.H. Aghaee-Bakhtiari, Androgen receptor-related micro RNAs in prostate cancer and their role in antiandrogen drug resistance, J Cell Physiol 235(4) (2020) 3222-3234.
[126] L. Zhang, X. Li, Y. Chao, R. He, J. Liu, Y. Yuan, W. Zhao, C. Han, X. Song, KLF4, a miR-32-5p targeted gene, promotes cisplatin-induced apoptosis by upregulating BIK expression in prostate cancer, Cell Commun Signal 16(1) (2018) 53.
[127] Y. Fujita, K. Kojima, R. Ohhashi, N. Hamada, Y. Nozawa, A. Kitamoto, A. Sato, S. Kondo, T. Kojima, T. Deguchi, M. Ito, MiR-148a attenuates paclitaxel resistance of hormone-refractory, drug-resistant prostate cancer PC3 cells by regulating MSK1 expression, J Biol Chem 285(25) (2010) 19076-84.
[128] J. He, M. Sun, H. Geng, S. Tian, Long non-coding RNA Linc00518 promotes paclitaxel resistance of the human prostate cancer by sequestering miR-216b-5p, Biol Cell 111(2) (2019) 39-50.
[129] Z. Xu, Y. Zhang, J. Ding, W. Hu, C. Tan, M. Wang, J. Tang, Y. Xu, miR-17-3p Downregulates Mitochondrial Antioxidant Enzymes and Enhances the Radiosensitivity of Prostate Cancer Cells, Mol Ther Nucleic Acids 13 (2018) 64-77.
[130] H. Gu, M. Liu, C. Ding, X. Wang, R. Wang, X. Wu, R. Fan, Hypoxia-responsive miR-124 and miR-144 reduce hypoxia-induced autophagy and enhance radiosensitivity of prostate cancer cells via suppressing PIM1, Cancer Med 5(6) (2016) 1174-82.
[131] R. El Bezawy, D. Cominetti, N. Fenderico, V. Zuco, G.L. Beretta, M. Dugo, N. Arrighetti, C. Stucchi, T. Rancati, R. Valdagni, N. Zaffaroni, P. Gandellini, miR-875-5p counteracts epithelial-to-mesenchymal transition and enhances radiation response in prostate cancer through repression of the EGFR-ZEB1 axis, Cancer Lett 395 (2017) 53-62.
[132] F. Wang, A. Mao, J. Tang, Q. Zhang, J. Yan, Y. Wang, C. Di, L. Gan, C. Sun, H. Zhang, microRNA-16-5p enhances radiosensitivity through modulating Cyclin D1/E1-pRb-E2F1 pathway in prostate cancer cells, J Cell Physiol 234(8) (2019) 13182-13190.
[133] R. Rupaimoole, F.J. Slack, MicroRNA therapeutics: towards a new era for the management of cancer and other diseases, Nat Rev Drug Discov 16(3) (2017) 203-222.
[134] N. Hosseinahli, M. Aghapour, P.H.G. Duijf, B. Baradaran, Treating cancer with microRNA replacement therapy: A literature review, J Cell Physiol 233(8) (2018) 5574-5588.
[135] A. Ganju, S. Khan, B.B. Hafeez, S.W. Behrman, M.M. Yallapu, S.C. Chauhan, M. Jaggi, miRNA nanotherapeutics for cancer, Drug Discov Today 22(2) (2017) 424-432.
[136] S. Boca, D. Gulei, A.A. Zimta, A. Onaciu, L. Magdo, A.B. Tigu, C. Ionescu, A. Irimie, R. Buiga, I. Berindan-Neagoe, Nanoscale delivery systems for microRNAs in cancer therapy, Cell Mol Life Sci 77(6) (2020) 1059-1086.
[137] P.K.B. Nagesh, P. Chowdhury, E. Hatami, V.K.N. Boya, V.K. Kashyap, S. Khan, B.B. Hafeez, S.C. Chauhan, M. Jaggi, M.M. Yallapu, miRNA-205 Nanoformulation Sensitizes Prostate Cancer Cells to Chemotherapy, Cancers (Basel) 10(9) (2018).
[138] F. Lin, D. Wen, X. Wang, R.I. Mahato, Dual responsive micelles capable of modulating miRNA-34a to combat taxane resistance in prostate cancer, Biomaterials 192 (2019) 95-108.
[139] A. Emmanouilidi, I. Casari, B. Gokcen Akkaya, T. Maffucci, L. Furic, F. Guffanti, M. Broggini, X. Chen, Y.Y. Maxuitenko, A.B. Keeton, G.A. Piazza, K.J. Linton, M. Falasca,

Inhibition of the Lysophosphatidylinositol Transporter ABCC1 Reduces Prostate Cancer Cell Growth and Sensitizes to Chemotherapy, Cancers (Basel) 12(8) (2020).
[140] S. Meidhof, S. Brabletz, W. Lehmann, B.T. Preca, K. Mock, M. Ruh, J. Schuler, M. Berthold, A. Weber, U. Burk, M. Lubbert, M. Puhr, Z. Culig, U. Wellner, T. Keck, P. Bronsert, S. Kusters, U.T. Hopt, M.P. Stemmler, T. Brabletz, ZEB1-associated drug resistance in cancer cells is reversed by the class I HDAC inhibitor mocetinostat, EMBO Mol Med 7(6) (2015) 831-47.
[141] T.M. Beer, S.J. Hotte, F. Saad, B. Alekseev, V. Matveev, A. Flechon, G. Gravis, F. Joly, K.N. Chi, Z. Malik, B. Blumenstein, P.S. Stewart, C.A. Jacobs, K. Fizazi, Custirsen (OGX-011) combined with cabazitaxel and prednisone versus cabazitaxel and prednisone alone in patients with metastatic castration-resistant prostate cancer previously treated with docetaxel (AFFINITY): a randomised, open-label, international, phase 3 trial, Lancet Oncol 18(11) (2017) 1532-1542.
[142] B. Jung-Hynes, M. Nihal, W. Zhong, N. Ahmad, Role of sirtuin histone deacetylase SIRT1 in prostate cancer. A target for prostate cancer management via its inhibition?, J Biol Chem 284(6) (2009) 3823-32.
[143] F. Saad, N. Shore, T. Zhang, S. Sharma, H.K. Cho, I.A. Jacobs, Emerging therapeutic targets for patients with advanced prostate cancer, Cancer Treat Rev 76 (2019) 1-9.
[144] Y. Bai, Z. Zhang, L. Cheng, R. Wang, X. Chen, Y. Kong, F. Feng, N. Ahmad, L. Li, X. Liu, Inhibition of enhancer of zeste homolog 2 (EZH2) overcomes enzalutamide resistance in castration-resistant prostate cancer, J Biol Chem 294(25) (2019) 9911-9923.
[145] N.G. Nickols, R. Nazarian, S.G. Zhao, V. Tan, V. Uzunangelov, Z. Xia, R. Baertsch, E. Neeman, A.C. Gao, G.V. Thomas, L. Howard, A.M. De Hoedt, J. Stuart, T. Goldstein, K. Chi, M.E. Gleave, J.N. Graff, T.M. Beer, J.M. Drake, C.P. Evans, R. Aggarwal, A. Foye, F.Y. Feng, E.J. Small, W.J. Aronson, S.J. Freedland, O.N. Witte, J. Huang, J.J. Alumkal, R.E. Reiter, M.B. Rettig, MEK-ERK signaling is a therapeutic target in metastatic castration resistant prostate cancer, Prostate Cancer Prostatic Dis 22(4) (2019) 531-538.
[146] K. Kojima, Y. Fujita, Y. Nozawa, T. Deguchi, M. Ito, MiR-34a attenuates paclitaxel-resistance of hormone-refractory prostate cancer PC3 cells through direct and indirect mechanisms, Prostate 70(14) (2010) 1501-12.
[147] X. Liu, X. Luo, Y. Wu, D. Xia, W. Chen, Z. Fang, J. Deng, Y. Hao, X. Yang, T. Zhang, L. Zhou, Y. Wu, Q. Wang, J. Xu, X. Hu, L. Li, MicroRNA-34a Attenuates Paclitaxel Resistance in Prostate Cancer Cells via Direct Suppression of JAG1/Notch1 Axis, Cell Physiol Biochem 50(1) (2018) 261-276.
[148] P. Gong, T. Zhang, D. He, J.T. Hsieh, MicroRNA-145 Modulates Tumor Sensitivity to Radiation in Prostate Cancer, Radiat Res 184(6) (2015) 630-8.
[149] R. El Bezawy, S. Tinelli, M. Tortoreto, V. Doldi, V. Zuco, M. Folini, C. Stucchi, T. Rancati, R. Valdagni, P. Gandellini, N. Zaffaroni, miR-205 enhances radiation sensitivity of prostate cancer cells by impairing DNA damage repair through PKCepsilon and ZEB1 inhibition, J Exp Clin Cancer Res 38(1) (2019) 51.
[150] Z.P. Cai, S.J. Tong, Y.P. Wu, L.X. Qu, Q. Ding, miR-181 regulation of BAX controls cisplatin sensitivity of prostate cancer cells, Int J Clin Exp Pathol 10(9) (2017) 10127-10133.
[151] M. Pennati, A. Lopergolo, V. Profumo, M. De Cesare, S. Sbarra, R. Valdagni, N. Zaffaroni, P. Gandellini, M. Folini, miR-205 impairs the autophagic flux and enhances cisplatin cytotoxicity in castration-resistant prostate cancer cells, Biochem Pharmacol 87(4) (2014) 579-97.
[152] E. Endzelins, V. Melne, Z. Kalnina, V. Lietuvietis, U. Riekstina, A. Llorente, A. Line, Diagnostic, prognostic and predictive value of cell-free miRNAs in prostate cancer: a systematic review, Mol Cancer 15(1) (2016) 41.
[153] X. Filella, L. Foj, miRNAs as novel biomarkers in the management of prostate cancer, Clin Chem Lab Med 55(5) (2017) 715-736.

[154] C. Hoey, S.K. Liu, Circulating blood miRNAs for prostate cancer risk stratification: miRroring the underlying tumor biology with liquid biopsies, Res Rep Urol 11 (2019) 29-42.
[155] H.L. Zhang, L.F. Yang, Y. Zhu, X.D. Yao, S.L. Zhang, B. Dai, Y.P. Zhu, Y.J. Shen, G.H. Shi, D.W. Ye, 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 71(3) (2011) 326-31.
[156] H.H. Cheng, P.S. Mitchell, E.M. Kroh, A.E. Dowell, L. Chery, J. Siddiqui, P.S. Nelson, R.L. Vessella, B.S. Knudsen, A.M. Chinnaiyan, K.J. Pienta, C. Morrissey, M. Tewari, Circulating microRNA profiling identifies a subset of metastatic prostate cancer patients with evidence of cancer-associated hypoxia, PLoS One 8(7) (2013) e69239.
[157] H.M. Lin, L. Castillo, K.L. Mahon, K. Chiam, B.Y. Lee, Q. Nguyen, M.J. Boyer, M.R. Stockler, N. Pavlakis, G. Marx, G. Mallesara, H. Gurney, S.J. Clark, A. Swarbrick, R.J. Daly, L.G. Horvath, Circulating microRNAs are associated with docetaxel chemotherapy outcome in castration-resistant prostate cancer, Br J Cancer 110(10) (2014) 2462-71.
[158] H.M. Lin, K.L. Mahon, C. Spielman, H. Gurney, G. Mallesara, M.R. Stockler, P. Bastick, K. Briscoe, G. Marx, A. Swarbrick, L.G. Horvath, Phase 2 study of circulating microRNA biomarkers in castration-resistant prostate cancer, Br J Cancer 116(8) (2017) 1002-1011.
[159] L. Bascetta, A. Oliviero, R. D'Aurizio, M. Evangelista, A. Mercatanti, M. Pellegrini, F. Marrocolo, S. Bracarda, M. Rizzo, The Prostate Cancer Cells Resistant to Docetaxel as in vitro Model for Discovering MicroRNAs Predictive of the Onset of Docetaxel Resistance, Int J Mol Sci 18(7) (2017).
[160] A.H. Zedan, P.J.S. Osther, J. Assenholt, J.S. Madsen, T.F. Hansen, Circulating miR-141 and miR-375 are associated with treatment outcome in metastatic castration resistant prostate cancer, Sci Rep 10(1) (2020) 227.