Non-coding RNAs in Prostate Cancer: From Discovery to Clinical Applications

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Yvonne Ceder

Abstract

Prostate cancer is a heterogeneous disease for which the molecular mechanisms are still not fully elucidated. Prostate cancer research has traditionally focused on genomic and epigenetic alterations affecting the proteome, but over the last decade non-coding RNAs, especially microRNAs, have been recognized to play a key role in prostate cancer progression. A considerable number of individual microRNAs have been found to be deregulated in prostate cancer and their biological significance elucidated in functional studies. This review will delineate the current advances regarding the involvement of microRNAs and their targets in prostate cancer biology as well as their potential usage in the clinical management of the disease. The main focus will be on microRNAs contributing to initiation and progression of prostate cancer, including androgen signalling, cellular plasticity, stem cells biology and metastatic processes. To conclude, implications on potential future microRNA-based therapeutics based on the recent advances regarding the interplay between microRNAs and their targets are discussed.

Keywords

MicroRNAs • Prostatic neoplasms • Androgen receptor • Epithelial-mesenchymal transition • Neoplasm metastasis

8.1 Introduction

Annually, close to 900,000 new prostate cancer cases are diagnosed worldwide making it the second most frequently diagnosed cancer in men, mainly affecting elderly men. Even though the incident is much higher in developed regions, the mortality is similar in developed and developing

Y. Ceder (✉)
Translational Cancer Research, Lund University, Medicon Village, Building 404:A3, 223 81 Lund, Sweden
e-mail: Yvonne.Ceder@med.lu.se

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regions, and constitutes the sixth leading cause of cancer related deaths in men (Ferlay et al. 2010). Prostate cancer is a multifocal and heterogeneous disease, making characterisation challenging (Arora et al. 2004). An in depth examination of the small non-coding RNA (ncRNA) content in prostatic tissues using next generation sequencing identified microRNA (miRNA), small nucleolar RNA (snoRNA), small nuclear RNA (snRNA), ribosomal RNA (rRNA), transfer RNA (tRNA) and fragments of large ncRNA (Martens-Uzunova et al. 2012). The most abundant class of ncRNA detected in the prostate was miRNAs, constituting 95 % of the RNA pool. The first systematic profiling of miRNAs in prostate cancer was presented by Porkka et al. in 2007, and since then several screening studies, and a multitude of individual expression analyses, have been published using different methodology (Volinia et al. 2006; Ambs et al. 2008; Ozen et al. 2008; Lu et al. 2005; Prueitt et al. 2008; Mattie et al. 2006; Tong et al. 2009; Martens-Uzunova et al. 2012; Szczyrba et al. 2010; Wach et al. 2012; Schubert et al. 2013; Porkka et al. 2007). The collective effort towards elucidating the function and mode of action of miRNAs in prostate cancer is increasing, and the impact of individual miRNAs on prostate cancer initiation and progression has been studied from different biological aspects (summarised in Table 8.1). The consensus is that ncRNAs may represent novel therapeutic targets and biomarkers for prostate cancer, but more basic research and clinical studies are needed. In this review, the main biological processes reported to be regulated by miRNAs will be outlined. This includes regulation of androgen signalling and the androgen receptor (AR), the transition to castration resistant prostate cancer (CRPC), cellular plasticity, stem cells and metastases. The best characterised miRNAs regulating these processes in the prostate, or miRNAs suggested to have therapeutic potential, will be presented together with ncRNAs used for diagnostic purposes.

Table 8.1 Regulatory miRNAs confirmed in studies of prostate cancer cells

miRNA	Chromosomal location	Function	Targets	References
Tumour suppressors				
miR-205	1q32	Proliferation, motility, invasion, EMT, adhesion	AR, PKC-ε	Hagman et al. (2013b) and Gandellini et al. (2009, 2012)
miR-133a	18q11, 20q13	Proliferation, invasion, migration	EGFR, PNP	Kojima et al. (2012) and Tao et al. (2012)
miR-143	5q32	Proliferation, migration	KRAS, ERK5, MMP13, FNDC3B	Xu et al. (2011), Clape et al. (2009), Fan et al. (2013), and Wu et al. (2013)
miR-145	5q32	EMT, motility, cell cycle, apoptosis	ERG, CCNA2, Oct4, c-Myc and Klf4	Hart et al. (2013), Ren et al. (2013), and Wang et al. (2009)
miR-16	3q25, 13q14	Apoptosis, proliferation	BCL2, CCDN1, WNT3a	Bonci et al. (2008)
miR-34a	1p36	Proliferation, EMT, stemness	AR, CD44, NOTCH,	Liu et al. (2011a), Ostling et al. (2011), and Kashat et al. (2012)
miR-34c	11q23	Proliferation, apoptosis, EMT, migration,	AR, E2F3, BCL2 and MET	Hagman et al. (2010, 2013a) and Ostling et al. (2011)
miR-200a	1p36	EMT	ZEB1/2	Kong et al. (2009)
miR-31	9q21	Apoptosis, cell cycle	AR, E2F1	Lin et al. (2013)
miR-124	8p23, 8q12, 20q13	Proliferation	AR	Shi et al. (2013)
miR-221	Xp11	Proliferation, androgen independence, migration	p27, HECTD2 and RAB1A, DVL2	Sun et al. (2014), Zheng et al. (2012), and Galardi et al. (2007)

(continued)

Table 8.1 (continued)

miRNA	Chromosomal location	Function	Targets	References
Onco-miRNAs				
miR-32	9q31	apoptosis	BTG2	Jalava et al. (2012)
miR-21	17q23	Invasion, EMT	RECK, BTG2	Coppola et al. (2013) and Reis et al. (2012)
miR-125b	11q24, 21q21	Apoptosis, proliferation	P53, puma, bak1, p14 (ARF), NCOR2	Amir et al. (2013), Yang et al. (2012), and Shi et al. (2011)
miR-106b	7q22	Apoptosis, cell cycle	Caspase-7, E2F1, p21	Hudson et al. (2013) and Ambs et al. (2008)
miR-141	12p13	AR activity, proliferation	Shp, JAG1	Xiao et al. (2012) and Vallejo et al. (2011)

8.2 Androgen Receptor

Androgen signalling through the AR is vital for the development and maintenance of the prostate, as well as governing the initiation and progression of prostate cancer. It has been shown that miRNAs are mediators of androgen action in the prostate and the existence of feedback loops between miRNAs, AR, and AR co-repressors, has been suggested (Narayanan et al. 2010). The AR seem to be able to act through different mechanisms in addition to the AR being recruited to the promoter of target genes, there also seem to exist a three-step pathway including miRNA activation, co-repressor suppression and DNA interaction. In LNCaP cells treated with siRNA against Dicer the induction of androgen-regulated prostate specific antigen (PSA) upon androgen stimulation was abolished, and tissue-specific knockout of Dicer in mouse models significantly reduced the activity of AR resulting in androgen insensitivity syndrome (Narayanan et al. 2010). The AR interaction with Dicer seems to be dependent on the conformational change brought upon by ligand interaction, indicating that the interaction between miRNAs and AR is signal specific. So far only a relatively modest number of miRNAs has been found to be regulated by androgens, compared to the large number of androgen-regulated mRNAs (Jalava et al. 2012; Hagman et al. 2013b; Ostling et al. 2011). In contrast, the regulation of AR seems to be complex. In a functional miRNA library screen using reverse phase protein array 71 unique miRNAs was found to affect AR levels in human prostate cancer cells (Ostling et al. 2011). Fifteen miRNAs down regulating AR, including miR-34a and miR-34c, was further confirmed to decrease androgen-induced proliferation. There are also several examples of indirect regulation of the AR activity e.g. the androgen-regulated miR-27a regulates the AR co-repressor prohibitin, and miR-21 and AR are involved in a positive feedback loop possibly through the phosphatase and tensin homolog (PTEN) (Fletcher et al. 2012; Mishra et al. 2014). Together this corroborates that miRNAs are important regulators of the AR and androgen signalling in normal prostate development, as well as in prostate cancer progression (summarized in Fig. 8.1).

8.2.1 miR-34 Family

The miR-34 family are known as master regulators of tumour suppression. The family is comprised of *mir-34a* located at chromosome 1p36, and *mir-34b* and *-c* clustered at chromosome 11q23. In prostate cancer, all miR-34 family members have been shown to be down regulated, and the expression of miR-34c correlates with the tumour grade, occurrence of metastases, and overall survival (Hagman et al. 2010; Kong et al. 2012). This down regulation has been linked to methylation of the CpG islands in the promoter of *mir-34a* and *mir-34b/c*, loss of het-

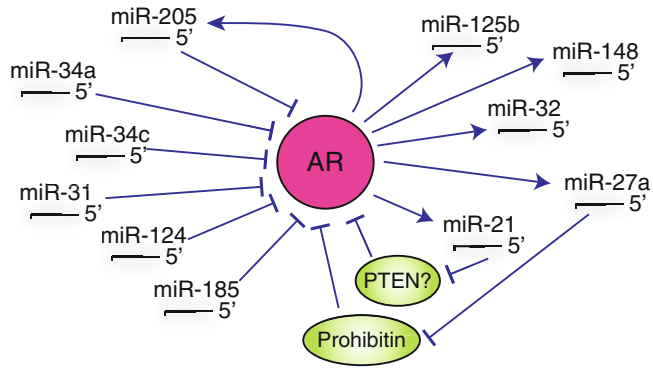

Fig. 8.1 Summary of miRNAs regulating AR and androgen regulated miRNAs (Qu et al. 2013a; Shi et al. 2007, 2013; Lin et al. 2013; Ostling et al. 2011; Hagman et al. 2013b; Jalava et al. 2012; Fletcher et al. 2012; Mishra et al. 2014)

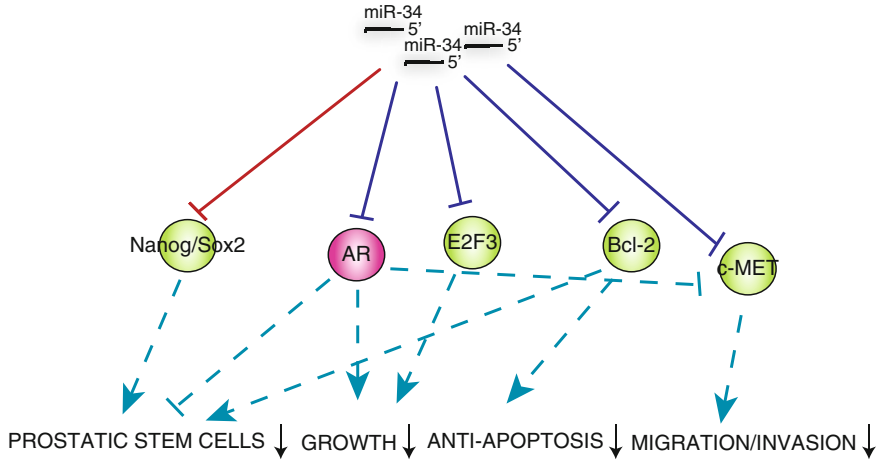

Fig. 8.2 The regulation of processes important for prostate cancer progression by the miR-34 family through key intermediates

erozygosity, and also direct regulation by the cellular tumour antigen p53 in response to DNA damage, hypoxia, and oncogenic stress, or by an alternative ATM-dependent pathway involving the p38-MAPK/MK2 pathway (Cannell et al. 2010; Toyota et al. 2008; Dahiya et al. 1997; Corney et al. 2007). Reconstituted levels of miR-34 can induce changes in proliferation, apoptosis, EMT and migration, and invasiveness of prostate cancer cells in vitro (Fig. 8.2). The family members have overlapping, but not identical targets. In prostate cancer cells, miR-34a has been shown to regulate AR, CD44, and NOTCH (Liu et al. 2011a; Ostling et al. 2011; Kashat et al. 2012), miR-34b regulates RAC-alpha serine/threonine-protein kinase (AKT) and the proto-oncogene protein MYC (Majid et al. 2013; Benassi et al. 2012), and miR-34c regulates AR, the apoptosis regulator BCL2, transcription factor E2F3, hepatocyte growth factor receptor cMET, and MYC (Hagman et al. 2010, 2013a; Ostling et al. 2011; Benassi et al. 2012). The miR-34 family has also been shown to be involved in epithelial-to-mesenchymal transition (EMT), caught up in a double negative feedback loop with Zinc finger protein SNAI1, and a similar feedback loop with the target ZEB1 (Siemens et al. 2011).

It has also been suggested that miR-34 acts as a barrier for somatic cell transition to stem/progenitor cells. Knockout mice of *mir-34a-c* show increased number of induced pluripotent stem cells and reprogramming efficiency without com-

promising self-renewal (Choi et al. 2011). In contrast, miR-34a also has been reported to decreased self-renewal capacity of prostate cancer cells (Kashat et al. 2012). It is possible the miR-34 family members individually have different functions that are modulated when the whole family is altered together. One hypothesis is that the expression of miR-34 family members is one of the mechanisms that keep the normal prostatic stem cells in control, but when the levels decrease upon prostate cancer initiation, the stem cell population is activated. Reintroduction of miR-34a or -b has been shown to significantly decrease androgen-independent prostate xenograft tumour growth in nude mice (Majid et al. 2013; Yamamura et al. 2012). In addition, miR-34a has been shown to reduce prostate cancer metastasis and increase the lifespan of xenografted mice (Liu et al. 2011a). Surprisingly, *mir-34a-c* knockout mice do not show increased effect on induced or spontaneous tumourigenesis (Concepcion et al. 2012). It is possible that this is due to the entire family being altered or that their function is compensated by other systems activated by the feedback loops the family is involved in.

8.3 CRPC

While confined to the prostate gland, the cancer is curable by either prostatectomy or radiation therapy. As the tumour progresses, it develops the abilities to invade surrounding tissue, induce angiogenesis, and metastasize. Androgen deprivation therapy, either chemical or surgical castration, is the gold standard treatment for advanced prostate cancer. Androgen depletion induces apoptosis of prostate cancer cells resulting in tumour regression, but this is followed by subsequent progression to castration resistance. To survive and resume growth in an androgen depleted surrounding, the cells must either adapt the AR pathway or induce alternative survival and growth pathways. Mechanisms underlying adaptation of the AR can be increased expression of AR, increased local production of androgens, hypersensitivity or constitutively active, truncated forms of the AR, promiscuity and/or ligand independent activation through kinase cross-talk. To bypass the AR pathway the epithelial cells might also be able to switch to autocrine production of growth factors such as epidermal growth factor (EGF), insulin-like growth factor (IGF1), hepatocyte growth factor (HGF), keratinocyte growth factor (KGF) or interleukin 6 (IL-6) (Jenster 1999). It has also been reported that individual miRNAs can promote androgen independent growth e.g. miR-21 (Ribas et al. 2009).

8.3.1 miR-21

The miRNA *mir-21* is an oncomiR located at 17q23.1, which is amplified in prostate cancer (Kasahara et al. 2002). The expression of miR-21 is induced by androgens through binding of the AR complex to its promoter region and is highly upregulated in CRPC (Jalava et al. 2012; Ribas et al. 2009). It has been reported that miR-21 promotes androgen resistance, but it is active in both androgen-dependent and -independent prostate cancer, and has been shown to stimulate prostate cancer xenograft growth in mouse models in both a ligand-dependent and -independent manner (Ribas et al. 2009). However, others report that ectopic expression of miR-21 only has a limited effect on cellular proliferation and invasiveness of prostate cancer cells, and contrary to in other cancer settings, miR-21 does not regulate the tumour suppressors PTEN and programmed cell death protein 4 (PDCD4) in prostate cancer cells (Folini et al. 2010). Nevertheless, it has been suggested that miR-21 has an effect on differentiation of prostate cancer cells as expression of miR-21 decreases B-cell translocation gene 2 (*Btg2*) levels, instigating the expression of luminal markers and a switch from epithelial to a mesenchymal phenotype in prostate cancer cells (Coppola et al. 2013). Hypoxia increases the expression of miR-21 and overexpression of miR-21 increases the levels of hypoxia-inducible factor 1-alpha (HIF1α) and vascular endothelial growth factor (VEGF), as well as AKT and extracellular signal-regulated kinase (ERK) through targeting of *Pten* leading to increased tumour angiogenesis (Liu et al. 2011b; Bao et al. 2012).

Another target of miR-21 is *Reck*, a known regulator of tumour cell invasion (Reis et al. 2012). In conclusion, miR-21 might contribute to the tumourigenesis by affecting several pathways leading to increased proliferation, EMT, angiogenesis and invasion. In addition, serum and plasma levels of miR-21 have been shown to be associated with aggressive prostate cancer, including castration resistant growth and metastases (Shen et al. 2012; Zhang et al. 2011; Yaman Agaoglu et al. 2011).

8.4 EMT and Cellular Plasticity

The transition from an epithelial to a mesenchymal phenotype plays a key role in prostate cancer progression. Tumour cells undergo EMT to be able to disseminate, yet the resulting metastases exhibit epithelial phenotypes. Hence, after seeding at the secondary sight, the cell has to undergo the reversal of EMT, i.e. mesenchymal-to-epithelial transition (MET), in order to proliferate and establish macrometastases. A finding supporting this plasticity scenario was reported in a murine prostate model in which 24 transcripts were compared in GFP-tagged PC3 primary tumour cells, circulating tumour cells (CTCs) and metastases. The primary and metastatic signatures were close to identical, whereas the CTCs signature stood out, for example *Bcl2* expression was increased in CTCs compared to the primary and metastatic tumour cells (Helzer et al. 2009). Disseminated metastatic cells can remain dormant for a variable period of time before forming secondary tumour sites. These secondary tumours may then shed novel metastatic cells to the blood stream resulting in multiple metastatic sites even if the primary tumour has been removed. It seems that the cells must exhibit phenotypic plasticity, a transient EMT-MET process, in response to the changing microenvironment as they invade through the basement membrane, enter and exit the circulation, and survive and grow at distant locations. Transcription factors, including SNAI1, SNAI2, TWIST and ZEB1/2, have been shown to regulate epithelial-mesenchymal plasticity. But recently, miRNAs have also been shown to be crucial regulators of EMT and cancer cell invasion. In fact, several studies suggest that cellular plasticity is governed by reciprocal feedback loops between miRNAs and their EMT-inducing targets (Fig. 8.3); e.g. the miR-200 family and ZEB1/2 (Burk et al. 2008; Bracken et al. 2008), miR-203 and SNAI1/2 (Qu et al. 2013b) and the miR-34 family and SNAI1 (Siemens et al. 2011). It is possible that these and similar feedback loops regulate the reversible phenotypic switch that allows tumour cells to exhibit EMT/MET plasticity in response to the microenvironment.

8.4.1 miR-200

The miR-200 family members have been described to act as tumour suppressors. As mentioned, miR-200 can repress expression of ZEB1 and ZEB2 transcription factors through direct tar-

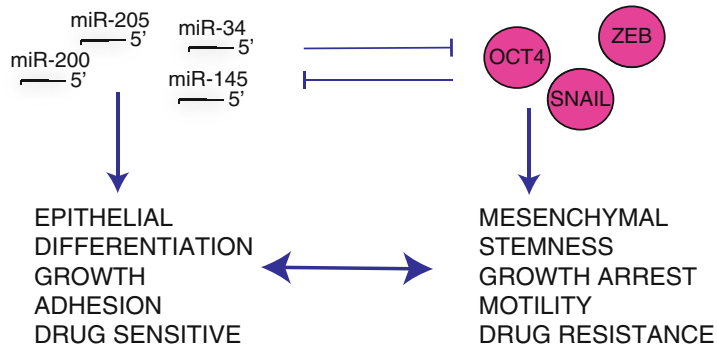

Fig. 8.3 Simplified illustration of the reciprocal feedback loops between certain miRNAs and their targets resulting in phenotypic plasticity

geting, leading to enhanced E-cadherin expression and inhibition of EMT. Conversely, ZEB1 and ZEB2 repress miR-200 expression by binding to the promoter of the *mir-200* encoding gene cluster, forming a double negative feedback loop controlling expressions of both during EMT. *Snai2* is another target of miR-200, and conversely SNAI2 is a direct repressor of miR-200 expression (Liu et al. 2013). In benign prostate cells, SNAI2 was found to be important for EMT initiation, while ZEB in cooperation with the miR-200 family opposed the reversal of the EMT (Slabakova et al. 2011). By preventing EMT, miR-200 prevents invasion and distant metastasis. Depletion of SNAI2 inhibits EMT during tumourigenesis, whereas reintroduction of miR-200 inhibited both EMT and tumourigenesis in human and mouse model systems (Liu et al. 2013). In concordance with these findings, decreased miR-200 expression has been associated with the acquisition of cancer stem cell traits and tumour-initiating capacity in other cancer settings. For example, the miR-200 family members also target Notch pathway components, such as *Jag1*, *Notch1*, mastermind-like gene 2 (*Mam2*) and *Mam3* (Brabletz et al. 2011; Kong et al. 2009). Further, it has been suggested that miR-200 plays a key role in linking the characteristics of cancer stem-like cells with EMT-like cells in prostate cancer. Cells with the EMT phenotype display stem-like cell features and decreased expression of miR-200, but re-introduction of miR-200 lead to reversal of EMT, reduced prostasphere formation, and expression of *Notch1* and *Lin28b* (Kong et al. 2009). It is possible that miR-200 is essential for cellular plasticity of cancer stem cells and hence of driving cancer progression towards metastasis. The levels of this potent molecule is tightly regulated by multiple reciprocal feedback loops with their targets and this might explain why miR-200 has not been found to be deregulated when identifying general expression patterns in larger prostate cancer cohorts (Porkka et al. 2007; Martens-Uzunova et al. 2012). However, in a study identifying the miRNA profile of primary prostate cancers using deep sequencing, miR-200c was found to be the most common transcript representing approximately 10 % of all miRNAs in pooled prostate cancer tissue (Szczyrba et al. 2010).

8.5 Stem Cells

The prostate contains a subpopulation of cells that do not depend directly on androgens for their survival; the prostate epithelial stem cells. Prostate stem cells are proposed to be present in the basal cell layer and, when dividing, give rise to another stem cell and a daughter progenitor cell/transit amplifying cell, which after a few divisions differentiate into end stage secretory luminal cells. They have the capacity to make the tumour recur from a single cell (Leong et al. 2008). Androgen deprivation therapy leads to expansion of the existing population of stem/progenitor cells (Lee et al. 2013). miRNAs, e.g. miR-145, have been suggested to play a central role in stem cell biology and regulate vital features such as self-renewal, pluripotency and differentiation. Further, exposure to increasing concentrations of chemotherapy has been shown to correlate to cancer stem cell-like traits and induction of EMT through downregulation of miRNAs such as miR-205 (Puhr et al. 2012).

8.5.1 miR-145

The intergenic *MIR145* is located on chromosome 5q32, and is co-transcribed with *MIR143*. The level of miR-145 is consistently reported to be decreased in prostate cancer (Larne et al. 2013; Wach et al. 2012; Ozen et al. 2008). A possible mechanism for the down regulation of miR-145 is methylation of the promoter as has been reported for the prostate cancer cell lines PC3, DU145 and LNCaP (Suh et al. 2011). miR-145 has also been suggested to be transcriptionally activated by p53, which frequently is mutated in advanced prostate cancer cells, and repressed by IL6, which is commonly up regulated in prostate cancer (Sachdeva et al. 2009; Suh et al. 2011; Zaman et al. 2010). Several reports also indicate that miR-145 is further decreased in metastatic prostate cancer, especially bone metastases

compared to localised prostate cancer (Leite et al. 2013; Peng et al. 2011). This agrees well with the described tumour suppressive functions of miR-145 in prostate cancer. It has been shown that miR-145 target oncogenic pathways such as C-myc (Sachdeva et al. 2009) and Ras (Kent et al. 2010), and is involved in the regulation of EMT and invasion (Peng et al. 2011; Guo et al. 2013). miR-145 also inhibits tumour growth and bone metastases of PC3 cells by repressing cancer stem cell properties in vivo, and in cooperation with miR-143, mir-145 supress prostatic tumour sphere formation and stemness markers in PC3 cells (Huang et al. 2012). Further, miR-145 inhibit stem cell renewal and pluripotency by targeting OCT4, SOX2 and Krueppel-like factor 4, and the reciprocal inhibition of miR-145 and OCT4 is believed to establish an irreversible switch priming cells to enter the differentiation program (Jain et al. 2012; Xu et al. 2009; Hu et al. 2012).

8.6 Metastases

Metastatic disease is the major cause of cancer-related deaths in men with prostate cancer, the 5 year survival rate is only 32 % compared to almost 100 % in localised early stages (Jemal et al. 2008). The development of metastases is a complex and dynamic process, involving detachment of the tumour cells from the primary site, entering and surviving in the bloodstream, migrating to distant locations where they extravasate and establish secondary tumours. Only a small fraction of the tumour cells in circulation give rise to distant metastasis, it has been suggested that cellular plasticity and transient acquisition of stem cell characteristics is necessary. The prostate cancer metastases are predominantly detectable in bone; autopsies reveal the presence of bone metastases in ~90 % of men with spread prostate cancer (Bubendorf et al. 2000). In bone, the prostate cancer induces the formation of lesions that are primarily osteoblastic in nature, causing the patient to experience severe bone pain and skeletal fragility. The prostate cancer cells at the metastatic site might still respond to androgen ablation but will also at the distant sites transform to CRPC. It has been shown that androgen deprivation therapy induces EMT and expansion of the existing population of stem cells, as a consequence the transition to CRPC is associated with increased incidence of metastases (Sun et al. 2012; Lee et al. 2013). While it is clear that the tumour microenvironment play a crucial role in determining the lethal phenotype of cancer cells, the molecular events associated with metastasis, homing to bone and colonization, invasion and survival at the secondary site are not well understood. It has been shown that miRNA expression in the primary tumour correlates to metastatic disease and also that a certain miRNA signature, the miRNA index quote (miQ), is an independent predictor of metastases events occurring 0.5–10 years after the removal of the primary tumour (Larne et al. 2013).

8.6.1 miR-205

The miR-205 encoding gene is located within the gene *LOC642587* of unknown function at chromosome 1q32, and has been shown to have decreased expression in prostate cancer (Majid et al. 2010; Gandellini et al. 2009). The miR-205 expression is regulated by p53, p63 and epigenetic silencing (Piovan et al. 2012; Wiklund et al. 2011; Hulf et al. 2013). In addition, the miR-205 expression is mainly localized to the basal epithelial cells, but as these cells disappear or differentiate during prostate cancer progression, this conceivably result in a loss of miR-205 expression (Gandellini et al. 2012; Zhang et al. 2010; Hagman et al. 2013b). It is reasonably a combination of these regulatory events that are responsible for the decrease of miR-205 levels corresponding to prostate cancer progression that is described in several independent studies (Majid et al. 2010; Gandellini et al. 2009; Hagman et al. 2013b). The expression of miR-205 is also inversely correlated to occurrence of metastases, castration resistant and shortened overall survival (Hagman et al. 2013b). In concordance with this, there are several reports indicating that miR-205 act as a tumour suppressor in prostate cancer

cells. miR-205 has been shown to directly regulate PKC-epsilon resulting in an effect on migration and invasiveness of prostate cancer cells (Wu et al. 2009). The expression of miR-205 decreases 100-fold when cells undergo EMT, but also contribute to EMT by targeting ZEB1/2, the transcriptional repressors of E-cadherin, this also contribute to enhanced migration (Gregory et al. 2008; Tucci et al. 2012). In addition, miR-205 has been shown to directly target the AR, a finding that was corroborated in a patient cohort were miR-205 expression inversely correlated to AR immunostaining in malignant prostate cells and to serum levels of the androgen regulated PSA (Hagman et al. 2013b). During prostate cancer progression, miR-205 levels decrease and this seem to result in activated AR signalling and increased migratory potential.

8.6.2 miR-15a/16

The first miRNA encoding genes identified to be frequently deleted in cancer was MIR15A and −16–1 located at chromosome 13q14 (Calin et al. 2002). They have also been found to be homozygously deleted in a subset of prostate cancers and to correlate with tumour progression (Porkka et al. 2011; Dong et al. 2001; Hyytinen et al. 1999). Loss of miR-15a/16 induce cellular proliferation in prostate cancer cells and restoration of miR-15a/16 result in growth arrest, apoptosis, and regression of prostate tumours in xenograft models (Cimmino et al. 2005; Bonci et al. 2008). These miRNAs promote apoptosis by targeting among others *Bcl2* (Bonci et al. 2008). Prostate luminal stem cells express *Bcl2* (Ceder et al. 2008) and it is plausible that miR-16 has an impact on the sensitivity to apoptosis in these cells. miR-15/16 have also been found to be down regulated in fibroblasts surrounding prostate tumours, and to repress fibroblast growth factor 2 (FGF2) and its receptor, which act on both stromal and tumour cells to enhance cancer cell survival, proliferation and migration (Musumeci et al. 2011). In a xenograph bone metastasis model, injection of miR-16 via the tail vein significantly inhibited the growth of prostate tumours in bone (Takeshita et al. 2010).

8.7 ncRNAs with Diagnostic Potential

A special characteristic of prostate cancer is that the latent form of the disease is very common; microscopic lesions are found in more than 50 % of 70–80 year old men (Gronberg 2003). However, most cases will never experience cancer symptoms during their lifetime. The current clinical practice for diagnosis and decision making of prostate cancer involve digital rectal examination, serum PSA and subsequent biopsies for histopathological staging and Gleason scoring. Each of these methods has its shortcomings and today a momentous problem is over diagnosis and treatment of patients with indolent prostate cancer. The management of prostate cancer would benefit from better tools for detection, prognosis and treatment response. The miRNAs are technically suitable as biomarkers as they are deregulated in prostate cancer, easy to detect and found to be stable in plasma, serum, fresh frozen, and formalin fixed paraffin embedded tissues. Many studies highlight the diagnostic and prognostic potential of individual miRNAs, however, no single miRNA has been consistently validated or implemented as a biomarker in clinical management of prostate cancer.

8.7.1 miRNAs Signatures

Lately several studies focusing on different miRNA signatures have been published. By extensive microarray analyses Martens-Uzunova et al. derived a miRNA diagnostic classifier that distinguishes prostate cancer from benign specimens; this classifier contains 54 miRNAs and gives an area under the curve of 0.95. The same team also constructed a prognostic signature consisting of 25 miRNAs that was able to independently predict postoperative outcome (Martens-Uzunova et al. 2012). Even smaller

number of prostate derived miRNAs has successfully been combined into quotes e.g. the miQ; ((miR-96×miR-183)/(miR-145×miR-221)), was found to successfully predict diagnosis with high accuracy in several independent cohorts, and also has prognostic power to predict aggressiveness of tumours, metastatic status, and overall survival (Larne et al. 2013). The advantage using a quote is increased discrimination, no need for housekeepings, and most important it may be an advantage considering the heterogeneity of the disease. There have also been preliminary data of non-invasive miRNA signatures that have prognostic properties e.g. miR-141 + miR151-3p + miR-16, that could discriminating between metastatic CRPC and localized prostate cancer in a cohort of 50 men (Watahiki et al. 2013). However, recent reports highlight the need for caution in the interpretation of the cancer-specificity of circulation miRNAs. It has been reported that 58 % of the published circulating miRNA biomarkers are highly expressed in hematopoietic cells, e.g. miR-16 is expressed in red blood cells, and that the levels of miR-21 and miR-141 in circulating are unaltered by radical prostatectomy raising questions of the origin of these miRNAs (Pritchard et al. 2012; Egidi et al. 2013).

8.7.2 *PCA3*

The only ncRNA that has made it all the way into clinical practice is the long ncRNA, prostate cancer antigen 3 (*PCA3*). *PCA3* is only expressed in the prostate, and it is highly overexpressed in 95 % of prostate cancer cells. Although the mechanisms of action are still unknown, *PCA3* has shown to be a useful prostate cancer biomarker. It can be detected by PCR in urine obtained after digital rectal examination (Bussemakers et al. 1999; Hessels et al. 2003). The urinary based test *PCA3*-to-PSA transcript has been approved for use in men suspected to have prostate cancer due to digital rectal examination and PSA but the first prostate biopsies is negative, as it has been shown to be useful to predict the presence of malignancy in this setting, and can thus reduce the number of unnecessary prostate biopsy (Haese et al. 2008; Marks et al. 2007). The *PCA3* score has also been shown to predict tumour volume, which might help in selecting prostate cancer patients for active surveillance (Ploussard et al. 2011).

8.8 Conclusions and Future Perspective

A decade ago small ncRNAs was first discovered to be involved in carcinogenesis (Chan et al. 2005; Calin et al. 2002). Now they are at the centre of attention and suggested to be suitable in the clinical management for most cancer forms. The miRNAs are promising biomarkers as they are deregulated, stable in both tissue and body fluids and easy to detect. As the technology will become even cheaper and more accessible the knowledge of the role of the ncRNAs and their potential applications will increase. It is conceivable that the miRNA signatures in circulating tumour cells or cancer-cell secreted microvesicles can enable personalized and patient tailored treatments for prostate cancer patients.

Individual miRNAs have evolved to coordinate the regulation of groups of molecules involved in essential cellular functions in the prostate. Prostate cancer progression is driven by not one but an array of genetic mutations and epigenetic alterations, individual miRNAs might provide a strategy to target systems rather than one molecule at a time in a fine-tuned manner. During the multi-step cascade of transient processes the tumour cells have to go through to enable e.g. metastatic spread, it is reasonable to speculate that reversible epigenetic modification is more likely to be regulating the balance between these events rather than fixed genetic alterations. In this context, it is interesting to note that the majority of miRNAs discussed in this review are epigenetically regulated. This also points to the very interesting interference option to reverse these processes by targeting the miRNAs.

However, it has lately become apparent that the miRNAs interact with their targets in more intricate manners than initially recognized. It has been discovered that many miRNAs are involved in both positive and negative feedback loops with their targets, hypothetically enhancing the robustness of gene regulation by creating a homeostasis between miRNAs and their targets. The tumour suppressor miR-34a is involved in a positive feedback loop with p53; miR-34a inhibits the expression of NAD-dependent protein deacetylase sirtuin-1 (SIRT1) that activates p53 (Yamakuchi and Lowenstein 2009). Loss or mutation of p53 is rare in primary prostate cancer but frequent in advanced cases. It is possible that reintroduction of miR-34a in the prostate cells with disturbed p53 function would lead to the expected tumour inhibition, but in adjacent cells with WT p53 it could potentially give negative long term effects of increased mutation rates leading to accelerated tumourigenesis. Then there is the heterogeneity of the 3′UTRs of the targets to take into considerations. It has lately been shown that over 50 % of all genes have alternative polyadenylation signals, and shorter 3′UTRs would lead to altered miRNA susceptibility in a specific setting (Tian et al. 2005). However, with increase knowledge about these changes, it is possible that this could be an advantage when designing specific gene targeting. Another factor complicating future miRNA based therapeutics might be target competition (Poliseno et al. 2010). Each miRNA targets several genes, as the levels of one of the targeted transcripts are increased in malignant tissues the available level of the inhibiting miRNA are decreased, and the repressive effect this is having on other transcripts might be relieved through target competition. This highlights the importance of targeted expression in the right setting and also the importance of selection of eligible patients. More in depth pre-clinical studies are needed to investigate the interplay between miRNAs and their targets in prostate cancer cells and the long term effects of manipulation of these delicate networks, as well as improved strategies for deregulation of the miRNAs in a prostate specific manner.

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