non-coding RNA

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Supplementary Materials

Regulation of Neuroendocrine-like Differentiation in Prostate Cancer by Non-Coding RNAs

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Supplementary Methods

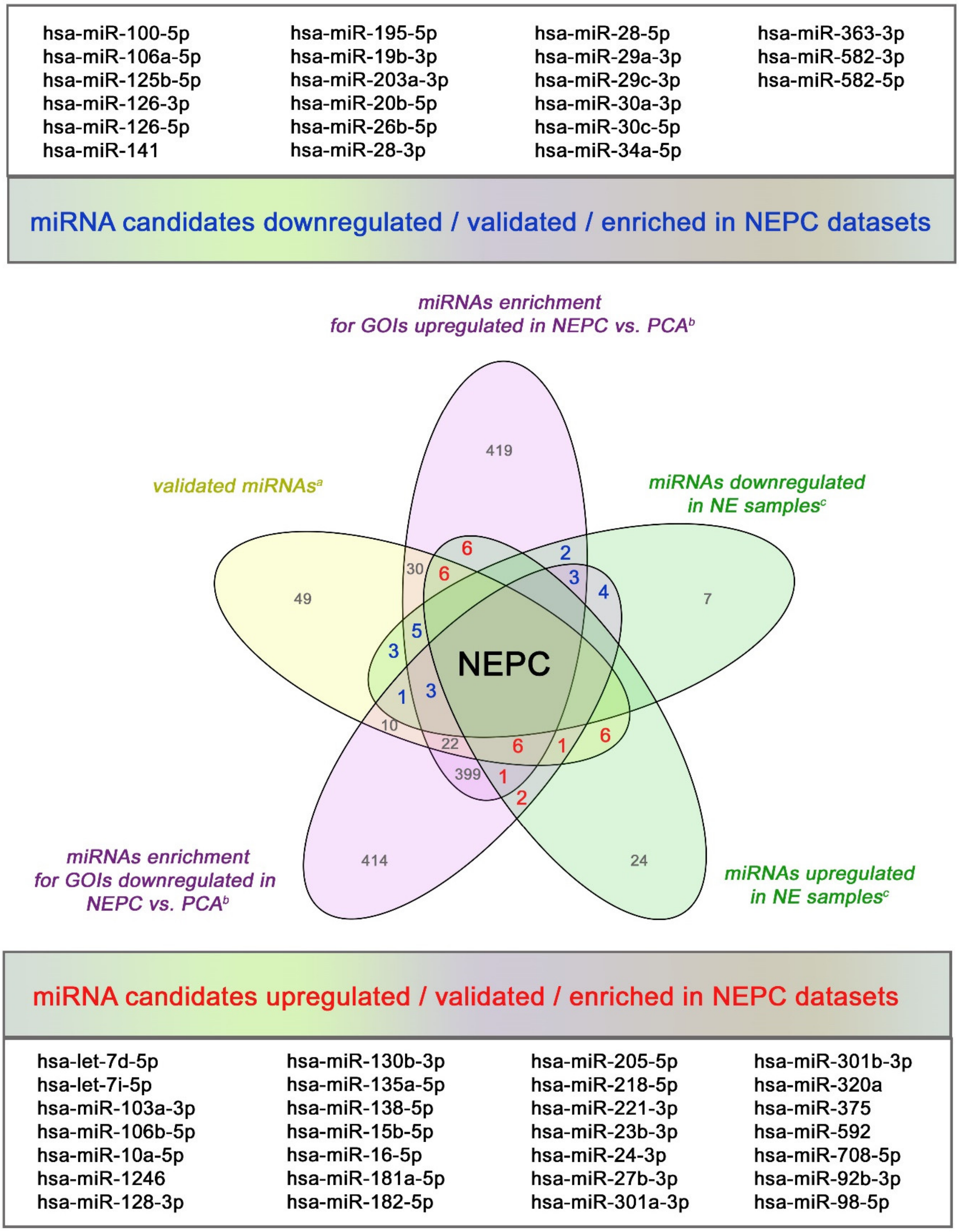
S1.1 Validated miRNAs targeting regulators and markers of neuroendocrine differentiation. Based on extensive literature mining, we identified genes encoding regulators and markers involved in neuroendocrine differentiation of prostate cancer (Supplementary Table 1). These genes were used as inputs for miRTarBase [1] in order to reveal validated miRNAs targeting their expression (in Supplementary Figure 1 assigned as "validated miRNAs").

S1.2 miRNA enrichment analysis of genes differentially expressed in samples of neuroendocrine prostate cancer vs. prostate adenocarcinoma. Using the Toppfun tool [2], we performed miRNA enrichment analysis of upregulated and downregulated genes identified in the RNA-seq study published by Beltran et al. [3] that were differentially expressed in the clinical samples of primary prostate adenocarcinoma and neuroendocrine prostate cancer. Genes with logFC values > 1.5 or < -1.5 and adjusted P value < 0.05 were used as an input geneset for the Toppfun tool. miRNA hits with Bonferroni p value < 0.05 were considered significant and were used for the identification of overlay between tested datasets (in Supplementary Figure 1 assigned as "enriched miRNAs").

Published dataset analyzed in this article

[3] Supplementary Table S3 in original manuscript—GOIs differentially expressed in NEPC vs. PCA clinical samples

[4] Supplementary Table S2 in original manuscript—miRNA genes differentially expressed in CRPC-NE vs. CRPC-Adeno clinical samples



Supplementary Figure S1. Candidate miRNAs involved in prostate cancer neuroendocrine differentiation**.** miRNA candidates related to the neuroendocrine prostate cancer (NEPC) development were identified across three distinct datasets. The first dataset of miRNA candidates was created through identification of miRNAs previously validated to target regulators and markers of NEPC by using miRTarBase [1]. Supplementary methods—S1.1; in Venn diagram geneset assigned by letter 'a'). Second dataset of miRNA candidates was derived from genes of interest (GOIs) previously identified by RNA-seq analysis comparing expression of genes differentially expressed between primary prostate adenocarcinoma (PCA) and neuroendocrine prostate carcinoma (NEPC) [3] (Supplementary methods—S1.2; in Venn diagram genesets assigned by letter 'b'). The third dataset of miRNA candidates originates from the study by Bhagirath et al., where genes encoding miRNAs differentially expressed between CRPC-NE vs. CRPC-Adeno clinical samples were reported [4] (in Venn diagram genesets assigned by the letter 'c'). miRNA candidates that were upregulated in NEPC-related datasets [4], experimentally validated to target selected regulators and markers of NEPC (our investigation) and, simultaneously, calculated as significantly enriched for geneset differentially expressed in NEPC vs. PCA samples [3], are summarized in lower table (in total 28; visualised in red). Similarly, miRNA candidates downregulated in NEPC-related datasets [4], experimentally validated to target selected regulators and markers of NEPC and, simultaneously calculated as significantly enriched for geneset differentially expressed in NEPC vs. PCA, are summarized in upper table (in total, 21; visualised in blue).

Supplementary Table S1. Regulators and markers of neuroendocrine differentiation in prostate cancer. Table shows selected genes chosen as targets for identification of experimentally validated miRNAs (miRTarBase; Supplementary methods—S1.1).

	Regulators and markers of NEPC
Abbreviation / Synonym	**Description**
hASH1/ ASCL1/ Mash1	Achaete-Scute Family BHLH Transcription Factor 1
AKT1	AKT Serine/Threonine Kinase 1
AR	Androgen receptor
BRN2 / POU3F2	POU Class 3 Homeobox 2
DCX	Doublecortin
DDC	Dopa Decarboxylase
EZH2	Enhancer Of Zeste 2 Polycomb Repressive Complex 2 Subunit
FOXA1	Forkhead Box A1
FOXA2	Forkhead Box A2
N-MYC / MYCN	Neuroblastoma MYC oncogene
NCAM1 / CD56	Neural Cell Adhesion Molecule 1
ONECUT2/ HNF6-beta	One cut homeobox 2
PTEN	Phosphatase and tensin homolog
PTHLH	Parathyroid Hormone Like Hormone
RB1	RB Transcriptional Corepressor 1
REST	RE1 Silencing Transcription Factor
SNAP25	Synaptosome Associated Protein 25
SOX2	Sex-determining region Y 2
Trop2 / TACSTD2	Tumor Associated Calcium Signal Transducer 2
TP53	Tumor Protein P53
TUBB3	Tubulin Beta 3 Class III

Supplementary Table 2. Cancer-related effects of NED-associated non-coding RNAs.

	Association with NED	Validated target			Expression in PCa	Cancer-related effect	Prognosis	Biomarker	Other findings
		NED marker	positive NED regulator	negative NED regulator	clinical samples	experimental findings	correlation with clinical data	source: indication	
1. miRNAs associated with neuroendocrine-like changes in prostate cancer models									
hsa-miR-17~92 cluster						• ↘ proliferation, migration, tumour growth, enhanced sensitivity to anti-androgens [5] • conveys chemoresistance [6]	• ↗ -> higher Gleason score, shorter BCR [7] • ↗ -> poor prognosis [8]	-	• seed sequence enriched in exosomal lncRNAs from PCa cells [9]
hsa-miR-17	• ↘ in experimental NED [10] • ↘ in NE-transformed LNCaP [11]	-	-	• RB1 [12] • PTEN [13] • TP53 [14]	• ↗ in solid tumours of different origin [15] • ↘ in high grade tumours [16] • associated with metastases [17]	• ↘ proliferation, ↗ apoptosis [18] • ↗ radiosensitivity [19] • ↗ proliferation, invasion, tumour growth [20] • modulates androgen signalling [21]	• extreme high and extreme low expression in aggressive disease [22] • high expression -> BCR [23]	• serum: PCa vs BPH [24]	• regulated by circITCH [25] and circ-MTO1 [26] • regulates mitochondrial antioxidant enzymes [27]

	Association with NED	Validated target			Expression in PCa	Cancer-related effect	Prognosis	Biomarker	Other findings
		NED marker	positive NED regulator	negative NED regulator	clinical samples	experimental findings	correlation with clinical data	source: indication	
hsa-miR-18a	-	-	-	• PTEN [28]	-	• ↗ proliferation [29] • ↗ tumorigenesis [30]	-	• plasma: healthy vs PCa [31] • blood: ↗ in advanced disease [32]	• regulated by lncRNAs GAS5 [33], • FENDRR [34], • PART1 [35]
hsa-miR-19a	• ↗ in the context of SOX4 upregulation [8]	-	-	-	-	• ↗ tumorigenesis [36] • prevents metastasis [37] • ↗ PCa progression [38] • regulates proliferation in CRPC [39]	-	• serum: predict adverse pathology [40] • urine: BCR prediction [41]	• ↗ by AR [42]
hsa-miR-20a	• ↘ in experimental NED [10] • ↗ in the context of SOX4 upregulation [8] • ↘ in NE-transformed LNCaP [11]	-	-	• RB1 [12] • TP53 [14]	• ↗ in solid tumours of different origin [15] • ↗ in advanced tumours [43–45] • ↗ in cancer vs healthy tissue [46]	• ↗migration, invasion [43] • ↗ tumour growth [47] • prevents apoptosis [48]	• change after docetaxel predicts survival [49]	• blood, plasma, serum: PCa vs non-cancer [45,50,51]	-
hsa-miR-19b	• ↘ in NEPC tissues [4]					-	• MYCN	• PTEN	

	Association with NED	**Validated target**			**Expression in PCa**	**Cancer-related effect**	**Prognosis**	**Biomarker**	**Other findings**
		NED marker	**positive NED regulator**	**negative NED regulator**	**clinical samples**	**experimental findings**	**correlation with clinical data**	**source: indication**	
							[52]	[53] • TP53 [54]	
hsa-miR-92a	-				-	-	• PTEN [55] • TP53 [14]	• ↘ [56,57] ↗ in solid tumours of different origin [15]	• ↘ viability, migration, invasion [56] • ↗ viability, migration, invasion [58] ↗ proliferation [59]
hsa-miR-663	• ↗ NED *in vitro* [60]	-	-	• TP53 [61]	-	-	• ↗ expression → clinical recurrence [60]	-	-
hsa-miR-32	• mediates enzalutamide-induced NED [62]	-	-	• PTEN [63]	• ↘ in blood [51] • enriched in exosomes from chemoresistant cells [64]	• ↗ cisplatin resistance [65] • ↗ proliferation and promotes transformation [66] • ↗ radioresistance [67]	-	• metaanalysis localized vs metastatic [68] • tissue: BPH vs CaP [69,70]	• regulated by AR [71]

	Association with NED	Validated target			Expression in PCa	Cancer-related effect	Prognosis	Biomarker	Other findings
		NED marker	positive NED regulator	negative NED regulator	clinical samples	experimental findings	correlation with clinical data	source: indication	
hsa-miR-204	• ⬀ with NED with tumour promoting effect [72]	-	-	-	• ⬂ in PCa [72] • ⬂ in advanced PCa [73] • ⬂ in tumours compared to adjacent tissue [74] • ⬀ in blood, ⬂ in cancer tissue [51]	• ⬂ migration, invasion, bone metastases [73] • ⬀ docetaxel sensitivity [75] • ⬀ apoptosis [76]	• ⬂ expression → poor prognosis [73]	• metaanalysis: PCa vs BPH [68] • urine: BCR prediction [77] • urine: isomiRs in healthy vs PCa [78] • tumour: primary vs metastatic [79]	• expression negatively regulated by androgens [72] • negative regulation by lncRNAs NEAT1 [80], UCA1 [81,82] • ⬀ AR, prevents TMPRSS2/ERG fusion [83] • ⬀ in exosomes in hypoxia [84]
hsa-miR-34a	• downstream effector in the AR-miR-204-XRN1 axis with tumour promoting effect on NED cells [72]	-	• MYCN [85] • SOX2 [86]	• AR [87] • TP53 [88]	• ⬂ in advanced tumours [89,90]	• ⬀ docetaxel sensitivity [91] • ⬂ IL-6 induced EMT and invasion [92] • ⬂ proliferation [93]	• ⬂ expression associated with poor prognosis [96]	• EVs *in vitro*: docetaxel resistance [97] • Metaanalysis: PCa vs BPH [68]	• negative regulation by lncRNAs NEAT1 [80], DANCR [98], LINC01006 and LINC00662

	Association with NED	**Validated target**			**Expression in PCa**	**Cancer-related effect**	**Prognosis**	**Biomarker**	**Other findings**
		NED marker	**positive NED regulator**	**negative NED regulator**	**clinical samples**	**experimental findings**	**correlation with clinical data**	**source: indication**	
						• ⇘ migration and invasion [94] • epigenetic silencing induces chemoresistance [95]			[99,100] • targets AR [87] • Frequent silencing by CpG methylation [101]
hsa-miR-221	• OE ⇨ NED of LNCaP [102]	-	-	• PTEN [103] • RB1 [104]	• ⇘ in PCa [105] [106,107] • ⇘ in advanced disease [108]	• sensitize to TRAIL [109] • ⇘ proliferation, migration, metastasis [105]	• associated with BCR [110] • ⇘ in recurrent PCa [111] • ⇘ expression associated with worse BCR free survival [112]	• plasma: ⇗ in PCa, less in advanced [102] • blood: localized vs metastatic [31]	-
2. miRNAs implicated in modulation of positive and negative regulators of NEPC									
hsa-miR-101	-	-	• MYCN [52]	-	• ⇘ in PCa [115] • ⇘ in metastatic PCa	• ⇘ prostate cancer cell growth [118]	-	• tissue: metastatic patients [120] • serum: ⇘ in PCa [121]	• regulated by lncRNA CRNDE [123]

	Association with NED	Validated target			Expression in PCa	Cancer-related effect	Prognosis	Biomarker	Other findings
		NED marker	positive NED regulator	negative NED regulator	clinical samples	experimental findings	correlation with clinical data	source: indication	
			• EZH2 [113,114]		[116,117]	• ↘ migration, invasion, tumour growth [119]		• putative biomarker of PCa metastasis [79,122]	• miR-101 biogenesis regulated by IFIT5 (downstream of IFNγ - antiviral response) [124] • expression modulated by androgen stimulation [125]
hsa-miR-27a	-	-	• AKT [126]	• TP53 [127]	• ↘ in metastatic PCa [116] • ↗ in PCa [128] • ↘ in PCa [129,130] • enriched in EVs of patients with advanced disease [131]	• contributes to chemoresistance [132]	• ↗ serum levels correlate with poor survival [128] • associated with metastases [17]	• serum: BPH vs CaP [133]	• regulated by androgen [42,129,134] • regulated by MYC [130] • regulated by lncRNAs PVT-1 [135] and ZFAS1 [136]
hsa-miR-30c-5p	-	-	-	• TP53 [137]	• ↘ in PCa and CRPC [138]	-	-	• urine: BPH vs PCa [140]	-

	Association with NED	**Validated target**			**Expression in PCa**	**Cancer-related effect**	**Prognosis**	**Biomarker**	**Other findings**
		NED marker	**positive NED regulator**	**negative NED regulator**	**clinical samples**	**experimental findings**	**correlation with clinical data**	**source: indication**	
					• ⬂ in PCa, associated with metastatic disease [139]			• urine: prediction of biopsy results [77] • tissue: BCR prognosis [141]	
hsa-miR-30c-1-3p	-	-	-	-	• ⬂ in PCa [142]	• ⬂ proliferation by restricting AR-V7 expression [142]	-	-	-
hsa-miR-30d-5p	-	-	• EZH2 [143]	• TP53 [144]	• ⬂ in PCa and CRPC [138]	• ⬂ cancer cell growth and invasion [145]	-	• seminal plasma: prediction of disease aggressiveness [146]	-
hsa-miR-31	-	-	-	-	• ⬂ in cancer tissue [147] • ⬂ in cancer, increasing in high grade [148] • ⬂ in primary cancer, increased in metastatic [149]	• ⬂ proliferation and invasion, induces apoptosis [150] • ⬂ tumour growth *in vivo* [151] • restores sensitivity to chemotherapy [152]	• promoter methylation promotes BCR free survival [153] • ⬂ expression associated with worse BCR free survival [112]	• extracellular vesicles: healthy vs BPH [154]	-
hsa-miR-346	-	-	-	-	-	• ⬀ AR activity through a novel and anti-dogmatic mechanism of direct association with AR 6.9	-	-	-
hsa-miR-361-3p	-	-	-	-	• ⬂ in recurrent cancer [156] • ⬀ in recurrent cancer [111]		-	-	-

	Association with NED	**Validated target**			**Expression in PCa**	**Cancer-related effect**	**Prognosis**	**Biomarker**	**Other findings**
		NED marker	**positive NED regulator**	**negative NED regulator**	**clinical samples**	**experimental findings**	**correlation with clinical data**	**source: indication**	
					• ↘ in CRPC [157]	kb 3'UTR and transcript stabilization [155]			
hsa-miR-197		-	-	-	• ↗ in CRPC cell lines [158] • ↗ in PCa tissues [159]		-	-	-
hsa-miR-644	-	-	• AKT [160]	-	-	-	-	-	-
hsa- miR-373-3p	-	-	• AKT [161]	-	• ↗ in high grade PCa [162]	• regulates invasion by TGF-β signalling [163] • ↗ migration and invasion [164]	-	-	-
hsa- miR-409-3p	-	-	• AKT [165]	-	-	• ↗ tumorigenesis, EMT, metastasis [166,167]	-	• plasma: CaP diagnosis [168] • serum: low risk vs CRPC [169] • serum exosomes: prediction of radiotherapy benefit [170]	

	Association with NED	**Validated target**			**Expression in PCa**	**Cancer-related effect**	**Prognosis**	**Biomarker**	**Other findings**
		NED marker	**positive NED regulator**	**negative NED regulator**	**clinical samples**	**experimental findings**	**correlation with clinical data**	**source: indication**	
3. lncRNAs associated with neuroendocrine-like changes in prostate cancer models									
lncRNA-p21	• ⬀ NSE, CgA, SYP [171]	• CgA, NSE, SYP [171]	• EZH2 [171]	-	• ⬀ in NEPC [171]	-	-	• urine: distinguish BPH from PCa [172]	• expression controlled by AR [171] • competes with lncRNA-HOTAIR in EZH2 binding [171]
lncRNA-PCAT6	• ⬀ NSE, CgA, and SYP [173]	-	-	-	• ⬀ expressed in NEPC [173]	-	• ⬀ expression predicts poor prognosis [174]	-	• ⬀ tumorigenesis by sponging miR-326 [173]
HOTAIR	• ⬀ in NE-like tumours [175] • positive correlation with CHGA [175]	-	• EZH2 [176]	-	• ⬀ in NED and CRPC [177]	• ⬀ migration and invasion by regulating hepaCAM [178] • ⬀ proliferation and invasion [179] • ⬀ stem-like phenotype and docetaxel resistance [180]	-	-	• regulated by REST [177] • ⬂ miR-193a [181] • regulated by androgens, stabilizes AR [179]
MALAT1	• ⬀ in NE-like tumours [175]	-	• cofactor of EZH2 [182]	-	• ⬀ expressed in PCa tumours [183] • ⬀ in PCa [184]	• ⬀ docetaxel resistance [185]	• ⬀ expression associated with poor survival [183]	• urine, plasma: PCa diagnosis [187–189]	• regulates miR-1 [190] • regulates miR-320 [190]

	Association with NED	**Validated target**			**Expression in PCa**	**Cancer-related effect**	**Prognosis**	**Biomarker**	**Other findings**
		NED marker	**positive NED regulator**	**negative NED regulator**	**clinical samples**	**experimental findings**	**correlation with clinical data**	**source: indication**	
							• enzalutamide treatment prediction [186]		• regulates miR-145-5p [185]
LINC00261	• ↗ in NEPC [191]	-	-	-	• ↘ in PCa [192]	• ↗ tumour formation and invasion [191] • ↗ by radiotherapy [193]	-	-	• drives NEPC through miR-8485-CBX2-FOXA2 [191]

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