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Expression Profiles and Mechanisms of microRNAs in Prostate Cancer

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Abstract

MicroRNAs are small non-coding RNA molecules with a length of 20 to 25 nucleotides. As gene expression regulators, microRNAs can completely or not completely complementarily bind with mRNA to inhibit translation or degradate mRNA. Aberrant expression of microRNAs is closely related to the occurrence, development, metastasis and prognosis of prostate cancer. Some microRNAs may promote cancerization, while others are tumor suppressors. In this review, we summarized the expression profiles of microRNAs in recent years, in particular, the data obtained by large-scale high-throughput technologies. We also summed up microRNAs which had the potential to be biomarkers of prostate cancer, and the mechanisms of microRNAs in the developmental progression of prostate cancer. The review provided medical and scientific researchers with an overview of the status and role of microRNAs in prostate cancer. In short, we summarized the expression profiles of microRNAs discovered in recent years and their roles and mechanisms in the occurrence and development of prostate cancer.

Key words: Meta-MicroRNAs; Prostate cancer; Expression profile; Biomarker

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Introduction

Prostate cancer (PCa) is a high incidence of male reproductive system malignancy all over the world. In 2017; 161,360 new cases were reported, and 26,730 patients died from PCa in America [1]. In China, the incidence of PCa and the threat to men's health are also increasing. At present, PSA (prostate specific antigen) test was most widely used to screen PCa patients in clinical practice, combined with imageological examination and fine needle puncture to diagnose PCa. For low-risk PCa, the treatment strategies were closely monitor and active surveillance. For patients with high-risk PCa, options were radical prostatectomy (RP), radiation therapy, and androgen deprivation therapy (ADT). However, in the advanced cases of castration resistance and metastases, patients would receive chemotherapy. Nowadays, nanoparticle delivery system has attracted great attention from the scientific community. Nanoparticles display infinite potential to increase anti-tumor efficacy of highly hydrophobic chemotherapeutic drugs, which makes them more attractive to provide the opportunities in targeted drug delivery [2,3].

microRNAs (miRNAs) are small conserved endogenous non-coding RNAs with the length of 20-25 nt, which regulate target genes by complementarily binding to the 3'-untranslated regions (UTR) of target mRNAs. It was estimated that each miRNA could regulate hundreds of target genes, and each mRNA could be bound by hundreds of different miRNAs. So, about 60% of coding genes were regulated by miRNAs encoded by 1% of human genome [4]. Nowadays, more than 4800 human mature miRNAs were reported in miRBase v22 (<http://www.mirbase.org/>). miRNAs may effect a wide variety of cellular processes, such as cell proliferation, differentiation, and apoptosis, etc. miRNAs may also participate in multiple cellular pathways in a variety of solid tumors by dual roles: Oncogenic miRNAs or tumor suppressor miRNAs.

The goals of this review are to summarize the expression

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profiles of microRNAs in PCa, and to identify the predictive biomarkers which may isolate the lethal or drug-resistant patients to reduce overtreatment and to improve personalized treatment effect.

The Expression Profiles Of Micrnas In Prostate Cancer

Previously, we scanned the miRNAs expression profiles in high-risk and low-risk PCa tissue samples using the second-generation sequencing and quantitative real-time PCR (qRT-PCR) technology [5]. The obtained results were summarized in **Table 1** together with other literatures' data [6,7]. Some of these miRNAs expression were controversial in different studies, while others were consistent in tissue and body fluid specimens, which were all marked in **Table 1**. Obviously, miRNAs with consistent results reported in all literatures could provide more valuable information. For example, miR-26a, miR-106a and miR-141 were up-regulated in PCa tissues and serum samples. In addition, the gene encoded a sort of miRNA may produce multiple mature miRNA products due to different splicing processes, and they often have the same target genes and synergistic effects. Currently, there were more than 300 miRNAs differentially expressed in PCa tissues, and 49 miRNAs detected in serum, 4 in urine samples (**Table 1**). These

differentially expressed data were collected from different studies screening various prostate samples, such as prostate cancer (PCa), benign prostate controls, castration resistance prostate cancer (CRPC) and hormone sensitive PCa, and metastatic PCa, etc.

Following the rapid development of new high-throughput technologies, such as whole-genome analysis, deep sequencing and microarray, in particular, single-cell genome/transcriptome sequencing, researchers may get the miRNAs expression data in specific time and space from these large-scale analyses.

microRNAs as biomarkers for prostate cancer

At present, a lot of studies have focused on the correlation between specific miRNA expression level and various clinical features of PCa, such as tumor stage, Gleason score, metastasis, biochemical recurrence and disease specific death, etc. We also conducted a meta-analysis to evaluate the application value of miRNAs as PCa biomarkers. Our results supported that miRNAs might distinguish the different states of PCa and predict the prognosis of PCa [8]. About 180 miRNAs related to the prognosis, recurrence and metastasis of PCa have been found and summarized in **Table 2**.

miRNAs were good biomarkers because they not only could noninvasively identify PCa, but also were stable in a variety of samples and could be detected in a variety of methods. In **Table**

Table 1: The expression profile of microRNAs in prostate cancer.

High-expression micro-RNAs	Tissue								Serum			Urine
	let-7a [^] /c	miR-7/7a [*]	miR-9#	miR-10b	miR-15b [^]	miR-16 [^] #	miR-17-5p	miR-20a/b#	let-7i	miR-9 [*]	miR-16#	miR-615-3p
	miR-21 [^] #	miR-22 [^]	miR-26a [^] #	miR-27a [^] #	miR-28-3p	miR-29b [^]	miR-30a [*] /d [^] /e [*]	miR-31 [^] #/-5p [^]	miR-20b#	miR-26a#	miR-34b#	miR-4316
	miR-32	miR-33a [^]	miR-34/a [^] #/c [^]	miR-92 [^]	miR-93 [^] #	miR-96 [^]	miR-100 [^] #	miR-101 [^]	miR-92a/b	miR-93#	miR-100#	-
	miR-106/a [^] #/b	miR-122	miR-125b [^] #/b-5p/-2#	miR-126 [^] #/-5p [^]	miR-129 [^]	miR-135b#	miR-138	miR-141#/-3p	miR-103	miR-106a#	miR-107	-
	miR-143 [^] #	miR-144/ [*]	miR-146b	miR-148a/b	miR-150	miR-151a-5p	miR-153	miR-154 [*]	miR-125b#	miR-139-5p	miR-141#	-
	miR-155	miR-181b [^]	miR-182#/ [*] /-5p#	miR-183	miR-184 [^]	miR-191	miR-193/a-5p	miR-194	miR-143#	miR-195#	miR-197#	-
	miR-198 [^]	miR-200b-3p/c [^] #	miR-203 [^] #	miR-205-5p [^]	miR-210#	miR-212 [^]	miR-215	miR-216a	miR-200a/b/c#	miR-205	miR-209	-
	miR-218 [^]	miR-221 [^] #/-30	miR-222#/-3p	miR-301a [^] #	miR-302 [^]	miR-335 [^] / [*]	miR-338#	miR-370	miR-210#	miR-221#	miR-223#	-
	miR-373	miR-374a/ [*] /b	miR-375#	miR-379	miR-423-5p	miR-483-5p	miR-486-5p [^] #	miR-542-3p	miR-328	miR-375#	miR-485-3p	-
	miR-556-5p	miR-592	miR-615 [^]	miR-629 [*]	miR-650	miR-663	miR-671	miR-940	miR-486-5p#	miR-516-3p	miR-574-3p	-
	miR-1260b	miR-1301/-3p	miR-1307	miR-1323	miR-17-92 [^]	miR-99 cluster [^]	miR-106b-25	miR-183 cluster	miR-636	miR-640	miR-766	-
	-	-	-	-	-	-	-	-	miR-874	miR-885-5p	miR-1207-5p	-
	-	-	-	-	-	-	-	-	miR-1274a	-	-	-

	let-7a [^] /d#/g	miR-1	miR-7-1*	miR-8	miR-15b [^]	miR-16 [^]	miR-17/-3p	miR-21 [^] #	miR-15a/16-1	miR-24#	miR-26b#	miR-205#
	miR-22 [^]	miR-23a#/b	miR-24#	miR-25	miR-26a [^] /a-5p/b#	miR-27/a [^] #	miR-28-5p	miR-29a/b [^] /c	miR-30c	miR-107#	miR-129#	miR-214
	miR-30d [^]	miR-31 [^] #/-5p [^]	miR-33a [^]	miR-34a [^] #/b#/c [^] /c-5p	miR-92 [^]	miR-93 [^]	miR-96 [^]	miR-98	miR-223#	-	-	-
	miR-100 [^]	miR-101 [^]	miR-106a [^]	miR-107#	miR-124#	miR-125/a-3p/b [^] #	miR-126 [^] #/*/-5p [^]	miR-128/a	-	-	-	-
	miR-129 [^] #	miR-130b	miR-132	miR-133b#	miR-140	miR-143 [^]	miR-145#/-5p#	miR-146a	-	-	-	-
	miR-148#	miR-149	miR-151a-3p	miR-152/-3p	miR-154	miR-181b [^] /b-1#/c#	miR-184 [^]	miR-186	-	-	-	-
	miR-187	miR-190a	miR-192	miR-193b	miR-195	miR-196b	miR-198 [^]	miR-199a/a-3p/b	-	-	-	-
	miR-200/b/b*/c [^] #	miR-203 [^] #	miR-204	miR-205#/-5p [^]	miR-206	miR-212 [^]	miR-218 [^]	miR-219-5p	-	-	-	-
	miR-221 [^] #	miR-223 [^]	miR-224	miR-296-5p	miR-301/a [^] #/b	miR-320/a [^] #	miR-331-3p	miR-335 [^]	-	-	-	-
	miR-339-5p	miR-376c	miR-378	miR-432	miR-449a#	miR-452/-5p	miR-486-5p [^] #	miR-490	-	-	-	-
	miR-491-5p#	miR-493-3p/5p	miR-494	miR-503	miR-511-3p	miR-519d/-3p	miR-520h	miR-532-3p	-	-	-	-
	miR-542-5p	miR-564	miR-605	miR-615 [^]	miR-628-5p	miR-631	miR-875-5p	miR-1256	-	-	-	-
	miR-1207-3p#	miR-1271	miR-1296	miR-3619-5p	miR-1-133a	miR-17-92a [^]	miR-99 cluster [^]	miR-200 cluster	-	-	-	-
Low-expression micro-RNAs	let-7f	miR-21#	miR-27h	miR-100/-5p	miR-122a	miR-125b [^] #	miR-133b#	miR-141 [^] #	miR-141#	miR-375#	miR-378*	-
miRNA in CRPC	miR-145#	miR-154*	miR-181a	miR-184 [^]	miR-195	miR-196a/b-3p	miR-221#	miR-222 [^] #	-	-	-	-
miRNA in ADPC	miR-361/-5p	miR-383	miR-424	miR-487	miR-488#	miR-582-5p	miR-616	miR-23b-24	-	-	-	-
High-expression in metastatic Pca	let-7/c#	miR-17-5p	miR-19b	miR-20a	miR-29b	miR-34	miR-92a	miR-125b [^] #	miR-409-3p	-	-	-
	miR-128b	miR-141 [^] #	miR-145-3p#/-5p#	miR-146a/b	miR-148a	miR-184 [^]	miR-198	miR-200b-3p/c	-	-	-	-
	miR-205	miR-222 [^] #	miR-331-3p	miR-663	miR-3654	miR-4638-5p	miR-4735-3p	miR-106b-25	-	-	-	-
High-expression in metastatic Pca	let-7c#	miR-10	miR-24	miR-26	miR-27	miR-30c	miR-100 [^]	miR-125b#	miR-451	-	-	-
	miR-126#	miR-129-3p	miR-141#	miR-152	miR-181/a [^] /b-1#/c#	miR-210-3p#	miR-218	miR-221#	-	-	-	-
	miR-222#	miR-224	miR-338#	miR-409-3p/-5p	miR-543	miR-590-5p	miR-1247-5p	miR-106b-25	-	-	-	-

Low-expression in metastatic PCa	miR-1	miR-21	miR-23b	miR-27b	miR-29b	miR-30b-3p/d-5p	miR-33a	miR-34b#	-	-	-	-
	miR-96	miR-100 [^]	miR-133a	miR-135a-1/b#	miR-141#/-3p	miR-143	miR-145#	miR-146a	-	-	-	-
	miR-154	miR-181a/b	miR-182#	miR-183	miR-188-5p	miR-193a	miR-200/a/b/c#	miR-203#	-	-	-	-
	miR-205	miR-373	miR-429	miR-449a#	miR-486-5p#	miR-508-5p	miR-520c	miR-573#	-	-	-	-
	miR-618	miR-675	-	-	-	-	-	-	-	-	-	-

Note: ADPC-Androgen-dependent prostate cancer; CRPC-castration resistant prostate cancer ; PCa-prostate cancer; [^]-microRNAs inconsistently reported in different papers; #-microRNAs detected in both prostate cancer tissues and serum/urine samples or microRNAs with mechanism studies were conducted.

2, we found that the miRNA biomarkers in serum, especially urine samples, were still insufficient, which would be the direction of scientific researchers' efforts. In addition, a large number of studies have begun to focus on multiple miRNAs combined with other indicators to jointly predict PCa and its prognosis, such as PSA (prostate specific antigen), PCA3 (prostate cancer antigen 3) and fusion gene TMPRSS2-ERG, etc. In **Table 2**, the miQ index was invented by Larne et al. [9]. It could differentiate PCa accurately and had the potential to predict prognosis [9]. This was also an effective strategy to avoid high heterogeneity of PCa.

THE Mechanism Of Micrnas In Prostate Cancer Progression

Most miRNAs are transcribed by RNA polymerase II, processed by Drosha and Dicer, and transported out of the nucleus by Exportin-5 during this period. Finally, the mature miRNAs become the 18-25 nt duplexes, assembled into the RNA-induced silencing complex (RISC). Moreover, most mature miRNAs combine with the 3'-UTR of the target messenger RNA, a few mature miRNAs bind to 5'-UTR. Some studies have shown that miRNAs can also combined to the coding regions or the specific sequence promoter of target genes [10-12].

The Mechanism Of Abnormal Expression Of Mirnas In Prostate Cancer

miRNAs have dual functions: oncogenic miRNAs can activate carcinogenesis, tumor suppressor miRNAs can inhibit tumor progression. Among them, carcinogenic miRNAs are usually highly expressed in PCa, while tumor suppressor miRNAs are down-regulated. In high-risk PCa and CRPC (Castration Resistant Prostate Cancer), the expression of Dicer and Drosha/DGCR8 was significantly increased, which contributed to the processing and up-regulated the expression of oncogenic miRNAs [13,14]. On the contrary, Drosha or Dicer expression decreased would attenuate mature miRNA biogenesis [15,16]. Myc could inhibit the binding of miR-26a/b to RNA polymerase II, thus affecting its transcription [17].

On the other hand, the genes that encoded tumor suppressor miRNAs were deleted in 60% of PCa samples [18,19]. Mutations or polymorphisms of tumor suppressor miRNAs might also lead to down-regulation of their expression, and increase the susceptibility to PCa [20,21]. In addition, methylation of the promoters of tumor suppressor miRNAs also reduced their

expression, increasing the risk of PCa [22-24].

In addition to the above mentioned mechanisms leading to abnormal miRNAs expression, it was worth mentioning that the absence or variation of target genes was also one of the important reasons for the development of PCa. Feng et al. found that the C/T polymorphism of BMPRI3 located in the 3'-UTR of this gene where was the binding site of miR-125b, could cause miR-125b not to bind to this region and lose its regulatory role, increasing the risk of cancer [25,26].

Micrnas Associated With Androgen Receptor Signaling Pathways

Early clinical PCa was mostly androgen-sensitive, but some of these cases would progress to incurable CRPC or metastatic PCa after initial treatment or ADT. These suggested that androgen receptor (AR) played an important role in the evolution of PCa. AR is a nuclear hormone receptor as a transcription factor to regulate the expression of a large number of downstream target genes. Previously, we had reviewed miRNAs related to AR signaling pathways [27]. In the review, we had not only summarized many miRNAs regulated by AR, but also gathered the miRNAs that directly and indirectly regulated AR [27].

Ostling et al. detected 71 miRNAs in a large sample study that affected AR expression levels by binding to AR 3'-UTR region of 6 Kb length [28]. miR-135b, miR-147, miR-34a, miR-644, miR-297, miR-298, miR-299-3p, miR-371-3p, miR-421, miR-449/b, miR-491-5p and miR-876-3p reduced AR mRNA levels, and miR-488 decreased AR protein levels, while miR-644 increased AR mRNA levels [28]. In addition, other research groups found that miR-34b [18], miR-124 [29], miR-145 [30], miRNA-221/222 [14], miR-301a [31], miR-320a [32] and miR-449a [33] could directly regulate AR expression and AR signaling pathway activity. miR-31 bound to the coding region of AR gene, which was usually mutated in PCa [34]. miR-1207-3p indirectly regulated AR activity through direct target molecule FNDC1 to form a new miR-1207-3p/FNDC1/FN1/AR pathway in PCa [35]. miR-185 could indirectly attenuate AR function by inhibiting BRD8 ISO2 [36]. Furthermore, miR-2909 and AR regulated each other to structure a positive feedback loop [37], while a negative feedback loop was formed between miR-124 and AR [38].

In addition to the above mentioned miRNAs that regulated AR, there were many miRNAs that were regulated by AR. Androgen could stimulate a variety of miRNAs expression, such as: miR-21

Table 2: MicroRNAs as biomarkers in prostate cancer.

Items	Tissue								Serum			Urine
	let-7a/b	miR-16#	miR-21#	miR-23b	miR-96	miR-106a	miR-141#	miR-149	let-7c#	miR-15a/16-1#	miR-19/b-3p	miR-145#
Diagnosis	miR-150	miR-182#	miR-185#	miR-187	miRNA-200c#	miR-205#	miR-221#	miR-222#	miR-21#	miR-30c	miR-34b#	miR-193b
	miR-224	miR-452	miR-551	miR-663	miR-1274	miR-2909#	miQ	miR-130b-301b	miR-129	miR-139-5p	miR-141#	miR-205#
	-	-	-	-	-	-	-	-	miR-151-3p	miR-200a/b/c#	miR-203	miR-214#
	-	-	-	-	-	-	-	-	miR-205#	miR-214#	miR-297#	-
	-	-	-	-	-	-	-	-	miR-320a#/b/c	miR-345	miR-375#	-
	-	-	-	-	-	-	-	-	miR-519c-5p	miR-2909#	-	-
	let-7a-1/a/f	miR-9#	miR-15b	miR-16	miR-21#	miR-24	miR-26a	miR-29a*	miR-19a#	miR-20a	miR-21#	-
Gleason score	miR-30d	miR-31#	miR-33	miR-34a*	miR-93	miR-96	miR-106a	miR-125b#	miR-141#	miR-200b	miR-221#	-
	miR-126*	miR-132	miR-143	miR-145#	miR-152	miR-182#	miR-195	miR-205	miR-375#	miR-451#	-	-
	miR-221#	miR-222#	miR-296	miR-331-3p	miR-342-3p	miR-425*	miR-451#	miR-551a	-	-	-	-
	miR-622	miR-708	miR-106b-25	-	-	-	-	-	-	-	-	-
	miR-18a-5p	miR-21#	miR-23b	miR-27b	miR-24	miR-29b	miR-34a#	miR-143	-	-	-	-
Treatment	miR-199a	miR-200c#	miR-210	miR-146a	miR-375#	miR-491-5p#	miR-17-92	-	-	-	-	-
	let-7b	miR-1	miR-10b	miR-15/b	miR-16	miR-21#	miR-23b	miR-24	miR-15a/16-1	miR-129	miR-146b-3p	-
	miR-30d	miR-31#	miR-34b#	miR-96	miR-100	miR-106b	miR-133b#	miR-135a/b#	miR-152	miR-194#	miR-375#	-
	miR-143	miR-151-3p	miR-182#/-5p#	miR-183	miR-187	miR-188-5p	miR-194#	miR-200a	miR-1290#	-	-	-
	miR-205	miR-210	miR-221#	miR-222#	miR-224	miR-301a#	miR-331-3p	miR-375#	-	-	-	-
Prognosis	miR-429	miR-449b#	miR-452	miR-511-3p	miR-516-3p	miR-708	miR-711	miR-940	-	-	-	-
	miR-1207-3p#	miR-2909#	miR-4638-5p	miQ	miR-106b-25	-	-	-	-	-	-	-
	let-7c#	miR-1	miR-16	miR-31#	miR-32	miR-33	miR-34a#/b#	miR-126*	miR-194	miR-628-5p	-	-
Metastasis	miR-141-3p	miR-143	miR-145#	miR-154*	miR-181a	miR-195	miR-205	miR-379	-	-	-	-
	miR-409-3p/-5p	miR-518f-5p	miR-573#	miQ	-	-	-	-	-	-	-	-

Note: #-microRNAs detected in both prostate cancer tissues and serum or microRNAs with mechanism studies were conducted; miQ=(miR-96-5p × miR-183-5p)/(miR-145-5p × miR-221-5p)

[39], miR-23a, miR-24-2, miR-27a [40], miR-19a, miR-133b [41], miR-125b [42], miR-148 [43], miR-182-5p [44], miR-126, miR-181b-l, miR-181c, miR-221, miR-338 [45] and miR-421 [46], and so on, androgen responsive element (ARE) might exist in these miRNAs flanking sequences. AR could also inhibit or activate the expression of miR-99a, let-7c and miR-125b-2 by chromatin remodeling factors: EZH2 or JMJD3 [47]. In addition, let-7d [48], miR-10a, miR-141, miR-15* and miR-1225-5p [49], were regulated by androgen.

MicroRNAs associated with metastatic prostate cancer and CRPC

Metastasis and castration resistance were two characteristics of advanced PCa. EMT (epithelial to mesenchymal transition) was the important performance of metastasis, while MET (mesenchymal to epithelial transition) was the phenotype of benign reversion of PCa. The researchers commonly used interdermal markers: fibronectin, ZEB1, ZEB2, vimentin, ZO1, snail and epithelial marker: E-cadherin, to monitor the occurrence and development of metastasis.

Osthole, a coumarin extracted from medicinal plants, inhibited EMT and metastasis by down-regulating the expression of miR-23a-3p to reduce E-cadherin expression and Snail DNA-binding ability [50]. Snail was also confirmed to be the target gene of miR-486-5p [51], miR-182 and miR-203 [52]. The members of miR-200 family, miR-200c and miR-141, inhibited JAGGED1 protein expression, and further regulated ZEB1 which was a mesothelial marker [22]. miR-210-3p participated in NF- κ B signaling *via* targeting TNIP1 and SOCS1 to trigger EMT, migration and bone metastasis [53]. miR-9 was an oncomiR targeting E-cadherin [54], while miR-573 was a tumor suppressor to directly target FGFR1 gene [55].

So far, metastatic castration-resistant prostate cancer (mCRPC) is considered incurable. miRNAs may play an important role in the malignant transformation process of PCa to this terminal stage. There was study finding that miRNA-221/222 was up-regulated in CRPC [14]. miR-145-5p and miR-145-3p were down-regulated in CRPC, and miR-145-3p had four downstream target genes: MELK, NCAPG, BUB1, and CDK1 [56]. In addition, miR-1290 and miR-375 might be the potential prognostic biomarkers for CRPC patients in exosomes [57].

Conclusion

As a group of small non-coding RNA molecules, microRNAs, combined with long non-coding RNAs, jointly regulate complex signal networks with different mechanisms. Are they subordinate or dominant in the occurrence and development of PCa? What are the mechanisms by which they contribute to PCa? These questions are far from being answered by researchers. We still need a lot of further researches to reveal the rules, and to provide the powerful theoretical basis for early diagnosis, prognosis prediction and targeted treatment for PCa.

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