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REVIEWS AND THEORETICAL ARTICLES

The Role of miRNAs in the Development of Prostate Cancer

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Abstract—MicroRNAs (miRNAs) act as key post-transcriptional regulators of gene expression. This review examines current advances in the study of the role of miRNAs in cancer, including prostate cancer. Issues devoted to the nomenclature, biogenesis, the role of miRNAs as oncogenes and tumor suppressors, and their role in the diagnosis, treatment, and prognosis of prostate cancer are discussed. Assessment of the role of miRNAs in the development of prostate cancer will promote early diagnosis and will be important for the development of new approaches to the disease treatment.

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INTRODUCTION

Prostate cancer (PC) is one of the most common cancers in men all over the world [1]. In 2012, there were 29082 new PC cases in Russia. Over at ten-year period (from 2002 to 2012), the increase in the absolute number of cases amounted to 119.6%. In the morbidity structure of the male population of Russia, PC is second (12.1%) after tumors of the bronchopulmonary system [2].

The exceptionally fast increase in the incidence of PC, which reaches about 3% per year, makes it possible to predict a doubling of the number of reported cases in 2030 [3].

For many years, the primary diagnostic test for PC was digital rectal examination (DRE). The introduction of the prostate specific antigen (PSA) screening in the blood serum into clinical investigation not only had a tremendous impact on the early diagnosis of the disease but also resulted in an increased incidence of documented prostate cancer [4]. The predictive value of the PSA concentration in serum is low. Despite the fact that PSA is considered a marker of diseases associated with prostate inflammation, it is not specific for prostate cancer. Serum PSA level can vary in the case of benign prostatic hyperplasia (BPH) and acute and chronic prostatitis. Moreover, the PSA level is affected by thyroid inflammation and pharmacological treatment, which can lead to overdiagnostis of prostate cancer [5, 6]. The PSA level does not correlate with cancer aggressiveness and cannot influence the choice of therapy. Due to the low predictive value of PSA screening, PC patients undergo invasive or radical procedures with considerable side effects [7]. If there are changes in PSA concentration, the patients undergo transrectal ultrasound (TRUS) and multifocal transrectal ultrasound-guided prostate gland (PG) biopsy, and the final diagnosis is based on pathological analysis of the PG biopsies.

At present, as a result of the application of a complex of modern methods for prostate cancer diagnosis, 47.7% of newly diagnosed cases of PC are diagnosed at stages I—II; 32.8% are found at a locally advanced stage (III stage); 17.4% are discovered at the metastatic (IV) stage of cancer [8]. However, mortality from PC in Russia remains high. For instance, cancer of the PG in 2012 caused 7.1% of all male deaths from cancer, ranking fourth in the structure of male mortality from cancer. Mortality in the first year after diagnosis of PG cancer in Russia in 2012 amounted to 10.3% on average [2].

Despite the significant advances in cancer research, early diagnosis, and treatment, the establishment of new markers and the creation of diagnostic panels of molecular markers with high accuracy and specificity that are able to predict tumor aggressiveness and disease prognosis in a particular patient is still an important problem. The resolution of this problem is necessary for early detection of malignant changes and the performance of the population screening to identify predisposition to the development of PC, as well as for disease prognosis and therapeutic decisions [7].

The discovery of a new class of noncoding RNAs-microRNAs (miRNAs), provided the emergence of a new direction in the early diagnosis of cancer [9, 10].

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It is known that most of the physiological processes are controlled by miRNAs. They are involved in the regulation of such cellular functions as the maintenance of stemness, differentiation, tissue development, apoptosis, and metabolism [9, 11].

Abnormal expression of miRNAs may have a significant influence on some specific features of cell biology, ultimately leading to various pathological phenomena, including cancer [9].

Since epigenetic regulatory mechanisms play a key role in the genesis and development of cancer and epigenetic events are the earliest in carcinogenesis, it is expected that the identification of miRNAs associated with the development of PC may not only shed light on the understanding of the molecular basis of pathogenesis of the disease but also provide for early diagnosis and serve as a basis to create new therapeutic targets for suppressing the aggressiveness of tumor cells.

This review focuses on the current knowledge on the mechanisms of miRNA action and an analysis of recent studies on the role of miRNAs in the development of cancer in general and prostate cancer in particular. Questions devoted to the nomenclature, biogenesis, the role of miRNAs as oncogenes and tumor suppressors, and their role in the diagnosis, treatment, and prognosis of prostate cancer are discussed.

GENERAL CHARACTERISTICS OF miRNAs

miRNAs are a class of small noncoding RNAs that consist of 18 to 25 nucleotides and interact with the 3' untranslated regions of target mRNAs in the cytoplasm [12–15]. Depending on the degree of base complementarity, they are involved in the regulation of expression of protein-coding genes causing either inhibition or degradation of target mRNAs at the post-transcriptional level [9, 12, 13, 15]. MicroRNAs are down-regulators of gene expression. Typically, for each miRNA, many targets can be predicted and vice versa; many genes carry potential recognition sites for different miRNAs [16]. It is known that hundreds of aberrantly expressed miRNAs are closely associated with the initiation and progression of most types of human cancers, and about 50% of microRNA genes are localized in fragile sites [17] and in the regions of the genome responsible for the development of cancer (loss of heterozygosity regions, genomic regions amplified in tumors) [13, 18]. In addition, from 20 to 40% of miRNA genes are located near the CpG islands, suggesting that they may be susceptible to epigenetic silencing, which is supported by studies of microRNAs in urologic cancers [17].

Mature miRNAs regulate the expression of up to 30% of human genes [19–21]. To date, almost two thousand miRNA genes and 2578 mature sequences were described in humans and annotated in the http://mirbase.org database. Human miRNA genes are evolutionarily conserved and distributed throughout the genome. They can be located in regions between the protein-coding genes and represent independent transcription units [22–24] or reside within the introns of protein-coding genes; their transcription then occurs in conjunction with pre-mRNAs of these genes [25, 26].

miRNA genes can be solitary or grouped in clusters. About a third of all miRNAs are clustered, and any change in the cluster can affect several miRNAs and involve thousands of protein targets. For example, the *MYC* oncogene transcriptionally activates the *miR-17-92* cluster, which is located on chromosome 13, for carcinogenesis initiation. In humans, there are several large miRNA clusters, including those on chromosomes 14q32 and 19q13 (>50 miRNAs in each). Many miRNAs have two or more duplicated genes that encode their mature RNAs. This redundancy ensures that the loss in one region hardly affects cellular activity and leads to upregulation of expression via the amplification of certain chromosomal regions [17].

miRNAs were initially discovered in 1993 while studying the *Caenorhabditis elegans* nematode [12, 15, 27]. The first discovered miRNA was named lin-4. The *lin-4* gene controls the larval stage of nematode development and encodes two RNA molecules of different lengths (22 and 61 nt). Structural comparison of these RNAs led to the conclusion that the longer molecule was able to form a hairpin and was the precursor of short RNA [28]. It was demonstrated that this small noncoding RNA molecule negatively regulated *lin-14* gene expression. In 2000, the second miRNA in *C. elegans*, let-7, which is also involved in the regulation of nematode larva development, was described [12, 29, 30]. Let-7 promotes the transition from the last instar larval stage to adult organism [31]. Over the past 12 years, considerable progress has been made in the study of miRNAs, which led to the discovery of about 4500 types of miRNAs in vertebrates, flies, worms, plants, and viruses. More than 1000 of these that were described in detail. It is expected that the number of these miRNAs will grow in the coming years [12].

The miRNA-mediated regulation of gene expression is different from that directed by transcription factors in the high rate of action, reversibility, and the ability to change locally the levels of target mRNA and proteins in certain cellular compartments [16]. MiRNAs play very important role in the regulatory potential of the genome. They are involved in the regulation of a large number of physiological processes of the organism from the moment of its appearance, such as tissue development [32], lipid metabolism, division, cell differentiation [33], apoptosis, and metabolism [12–14, 16].

MicroRNA NOMENCLATURE

According to the generally accepted rules of nomenclature, microRNAs are named with the prefix miR and a unique identification number (for example, miR-1, miR-2...,miR-89, etc.). The prefix miR is sep-

arated by a hyphen and is followed by the sequence number that is assigned in accordance with the discovery of miRNA, regardless of the type of organism. Given the type of organism from which miRNA was isolated, each name is preceeded by a three-letter prefix; for example, hsa-miR-101 and mmu-miR-101 indicates that these miRNAs were isolated from the cells of *Homo sapiens* and mouse, respectively.

miRNAs with identical structures get identical names. For example, the miR-1 of *Drosophila melanogaster* differs in a single nucleotide from miR-1 of *Caenorhabditis elegans* and humans. The miRNA sequences with differences at additional (one or two) nucleotides are annotated by additional alphabetic or digital indices (for example, miR-13a and miR-13b; miR-6-1 and miR-6-2 in *D. melanogaster*). The name is also complicated when different regions of one precursor give rise to different miRNAs (for example, miR-17-5p and miR-17-3p) [34, 35].

MicroRNA BIOGENESIS AND THE MECHANISM OF ACTION

In mammals, more than 90% of microRNAs are encoded by nucleotide sequences located in introns. For comparison, this value constitutes 14% in worms and flies [35]. miRNA biogenesis consists of several stages. At the initial stage, miRNA genes are transcribed by RNA polymerase II, resulting in the formation of precursor miRNAs (pre-miR) that contain from several hundred to several thousand nucleotides. The next stage is catalyzed by ribonuclease III (Drosha) and the RNA-binding protein Pasha (DGCR8), resulting in the cleavage of the miRNA precursor and the formation of the primary miR (pre-miR), which usually consists of about 70 nucleotides [12, 35–37]. The nuclear transporter factor, exportin-5, subsequently binds to the pre-miR and translocates it into the cytoplasm, where another RNAse, Dicer, interacts with the pre-miR, resulting in the formation of mature RNA duplex consisting of about 22 nucleotides [12, 37–39]. Mature miRNA in the complex with the Argonaut (Ago2) and TRBP family proteins forms RISC (RNA-induced silencing complex). One of the miRNA duplex strands (passenger strand) is degraded, and the functional strand activates RISC complex and interacts with target mRNA, resulting in the degradation of the latter, or translational inhibition [21, 37, 39, 40]. Imperfect binding leads to poor contact between the microRNA and target mRNA with subsequent inhibition of translation, while a high degree of complementarity promotes strong binding and proteolytic cleavage of target mRNA with the involvement RISC complex [38].

THE ROLE OF miRNA IN THE DEVELOPMENT OF CANCER

It is now established that miRNAs regulate the expression of more than 30% of the genes that encode protein structure and play an important role in numerous metabolic and biological processes. It is suggested that miRNAs may serve as new biomarkers in the diagnosis of cancer and become a target for therapeutic intervention. In recent years, numerous studies were conducted to determine miRNA expression profiles to identify specific microRNAs for a particular malignancy [36].

The participation of miRNAs in the development of cancer was first described for two miRNA genes, miR-15a and miR-16-1, located in the 13q14 chromosomal region in a study of B-cell chronic lymphocytic leukemia [17, 36]. The expression of these miRNAs is suppressed in about 80% of PC cases. The loss of miR-15a/16-1 increases the expression level of cyclin D1 protein, which is involved in the regulation of the transition from G1 to S phase. These miRNAs also affect the *WNT3a* gene, and their loss facilitates the activation of the precancerous Wnt-signaling pathway [17]. In fact, miR-15a and miR-16-1 induce apoptosis by affecting the *BCL2* gene product [36]. New data show a clear distortion of miRNA regulation in PC. As was demonstrated in six trials, miR-23b, miR-34a, miR-100, miR-145, and miR-205 were characterized by lower expression in tumor tissues in PC as compared to control. Interestingly, in five of these trials, miR-221 and miR-222 were aberrantly expressed in tumor tissues [21].

Numerous studies showed in most of cancer cases that there were significant changes in miRNA expression. For example, Volinia et al. [41] conducted a large-scale study and showed that miR-21, miR-191, and miR-17-5p were overexpressed in all of the examined solid tumor samples. In this study it was also demonstrated that the expression profiles of miR-125b, miR-145, and miR-21 were changed in breast tumors; the profiles of miR-103, miR-155, and miR-204 were changed in pancreatic tumors. Lu et al. [42], analyzed the expression of 217 miRNAs in 334 different tissue samples, including human cancers. It was demonstrated that miRNA expression levels were different in tumors of different origin, as well as in samples of tumor and normal tissue. A number of miRNAs with differential expression level were determined, including miR-20, miR-181a, miR-15a, miR-16, miR-17-5p, miR-221, let-7a, and miR-2. Most of these miRNAs were characterized by decreased expression levels in tumors as compared with normal tissues [42]. MicroRNA expression profiles were also described in lung cancer, colon cancer, glioblastomas, lymphomas, hepatocellular carcinomas, and other tumor types [36].

Functional studies showed that microRNAs with increased expression in tumor tissues can be regarded as oncogenes [37] and that the targets of their inhibitory action are, in most cases, genes coding for tumor suppressor proteins [43] or genes controlling cell cycle, differentiation, and apoptosis [13]. On the other hand, the expression of some miRNAs in tumors is decreased. It is believed that these miRNAs act as

Table 1. miRNAs with altered expression in cancer diseases

Tumor type	Increased expression	Decreased expression	References
Breast cancer	miR-21, miR-29b-2	miR-125b, miR-145, miR-10b, miR-155, miR-17-5p, miR-27b	[44, 45]
Ovarian cancer	miR-141, miR-200(a–c), miR-221	let-7f, miR-140, miR-145, miR-199a, miR-424	[46]
Endometrial cancer	miR-103, miR-107, miR-185, miR-205, miR-210, miR-449	miR-99b, miR-152, miR-193, miR-204, miR-221, let-7i	[46]
Glioblastoma	miR-221, miR-21	miR-181a, miR-181b, miR-181c	[41, 47]
Chronic lymphocytic leukaemia		miR-15, miR-16	[48]
Lymphoma	miR-155, miR-17-92 cluster	miR-15a	[42, 47]
Colorectal cancer	miR-10a, miR-17-92 cluster, miR-20a, miR-24-1, miR-29b-2, miR-31	miR-143, miR-145, let-7	[41, 42, 47]
Thyroid cancer	miR-221, miR-222, miR-146, miR-181b, miR-221, miR-222, miR-146, miR-181b, miR-197, miR-346		[41, 47]
Hepatocellular cancer	miR-18, miR-224	miR-199a, miR-195, miR-200a, miR-125a	[41, 47]
Testicular cancer	miR-372, miR-373		[42]
Pancreatic cancer	miR-221, miR-376a, miR-301, miR-21, miR-24-2, miR-100, miR-103-1.2, miR-107, miR-125b-1	miR-375	[42, 47]
Cholangiocarcinoma	miR-21, miR-141, miR-200b		[41]
Prostate cancer	let-7d, miR-195, miR-203, miR-96-5p, miR-183-5p	miR-128a, miR-145-5p, miR-221-5p	[7, 42, 46]
Gastric cancer	miR-223, miR-21, miR-103-2	miR-218-2	[42, 47]
Lung cancer	miR-17-92 cluster, miR-17-5p	Family let-7	[41, 42, 47]

tumor suppressors, preventing tumor development by inhibiting oncogenes or genes controlling either cell differentiation or apoptosis (Table 1) [36].

It should be noted that some microRNAs have different expression profiles in different types of cancer [49]. Furthermore, miRNA expression profile changes with tumor development. In this regard, the identification of microRNAs aberrantly expressed in various cancers is one of the urgent problems of modern biology and medicine.

In recent years, the number of newly identified microRNAs increased dramatically, but their biological role is still poorly understood. The analysis of global miRNA expression profiles in malignant tumors may contribute to the development of new methods for early diagnosis of many cancers, including PC, and to the determination of the disease prognosis.

THE ROLE OF miRNA IN PROSTATE CARCINOGENESIS

The functions of miRNAs are disturbed in every type of cancer. The nature of these disturbances is very different [37]. For example, miRNA can exert a negative effect by altering the expression level by either a loss or increase in the affinity of miRNA sequences within or on its target. The miRNA function is largely determined by the relative accessibility of the target mRNA. For these reasons, individual miRNAs may have different effects in tissues, especially in cancers of different cellular origin [12, 15].

Porkka et al. [50] conducted the first study on the expression profiles of 319 miRNAs in prostate cancer with oligonucleotide array hybridization and found differential expression of 51 miRNAs. However, not all of the results of Porkka et al. were confirmed by further research.

At present, the number of platforms developed for the study of the miRNA expression profiles is rapidly increasing. For the analysis of tumor-specific microRNAs, microarrays are often used. However, this method was based on previously accumulated data on miRNAs. The advent of next-generation sequencing (NGS) provided a new approach to identify previously unknown miRNAs. The most appropriate method to confirm the miRNA expression profile is real-time quantitative PCR (RT-qPCR) [36].

ONCOGENIC miRNAs IN PROSTATE CANCER

In malignant tumors of various origins, the expression of most miRNAs is reduced. This is consistent with the existing view of the association between miRNA expression and differentiation. However, microRNAs with amplified genes may have the functions of oncogenes. A number of these miRNAs were identified, as well as the well-known fact regarding the overexpression of oncogenic miR-181b in prostate cancer. He et al. [51] demonstrated that the inhibition of miR-181b induced apoptosis in the prostate cancer cells. Reis et al. [52] suggested that miR-21 negatively regulated *RECK*, a matrix metalloproteinase regulator, thereby providing the expression of the invasive properties of prostate cancer cells. In addition, miR21 can promote the development of the aggressive potential of prostate cancer cells through the regulation of other tumor inhibitors, such as MARCKS protein (Myristoylated alanine-rich protein kinase c substrate), which is the target of miR-21 [53]. There are other tumor suppressor genes negatively regulated by miR-21, including *ANP32A* and *SMARCA4* genes [54]. Since miR-21 is overexpressed in prostate cancer, targeted inhibition of miR-21 restores apoptosis in the cells [53]. It should be also mentioned that the transfection of miR-21 into prostate cancer cells induces resistance to the antitumor drug docetaxel [55].

It is known that the miR-106b-25 cluster is located in intron 13 of the *MCM7* gene (Minichromosome maintenance protein 7). The coexpression of *MCM7* and miR-106b-25 mediates prostatic intraepithelial neoplasia in transgenic mice. Moreover, *PTEN* expression is negatively regulated by miR-106b-25 [56]. It is interesting that miR-106b-25 regulates the *ZBTB4* (zinc finger and BTB domain-containing 4) at the post-transcriptional level. *ZBTB4* functions as a tumor suppressor gene and is involved in the inhibition of specific target gene expression by competitive binding with the promoter regions [57]. The miR-106b-25 cluster also negatively regulates capsase-7 [58]. There are conflicting data on the regulation miR-125b via androgen signaling. It is suggested that androgen receptor (AR) inhibits miR-125b to initiate the expression of various mRNA transcripts [59]. In contrast to these data, it was reported in one of the studies that androgen signaling stimulated miR-125b expression, while targeted inhibition of miR-125b led to a decrease in androgen-independent growth [60]. Moreover, miR-125b negatively regulates various proapoptotic genes, including *p53*, *Puma*, and *Bak1* [61].

TUMOR SUPPRESSORS IN PROSTATE CANCER

miR-15a and miR-16 function as a tumor suppressors by participating in the regulation of the expression of such oncogenes as *BCL2*, *MCL1*, *CCND1*, and *WNT3A* [12, 17]. It was reported that the injection of a new class of miRNA inhibitors, named antagomirs, in normal mouse prostate with the purpose of miR-15a and miR-16 silencing resulted in considerable hyperplasia [12, 17, 62] and an increase in survival, proliferation, invasiveness, as well as increased cancer disease severity in the immunodeficient NOD-SCID mice [17]. There is evidence that these microRNAs are expressed at low levels in many malignancies, including chronic lymphocytic leukemia, pituitary adenoma, and carcinoma of the prostate. In humans, miR-15a and miR-16 are located in the 13q14.3 region of chromosome 13, where, according to the literature, deletions occur not only in prostate cancer but also in such cancers as chronic lymphocytic leukemia, pituitary adenoma, mantle cell lymphoma, and prostate cancer. Aqeilan et al. [63] showed that the expression of miR-15a and miR-16-1 was considerably decreased in 80% of the examined prostate cancer samples as compared to normal tissues.

It is also known that expression of miR-224, miR-16, miR-31, miR-125b, miR-143, miR-145, miR-149, miR-181b, miR-184, miR-205, miR-221, and miR-222 is decreased in prostate cancer [17]. miR-143 and miR-145 play an important role in the biology of prostate cancer and act as tumor suppressors by inhibiting cell growth and activation of apoptosis [64].

miR-205 is a tumor suppressor, and its expression is increased in prostate cancer cells. The transfection of miR-205 in prostate cancer cells induces apoptosis. Note that miR-205 is directly involved in stimulating the expression of the *IL24* and *IL32* tumor suppressor genes [65]. This miRNA also participates in down-regulation of *Bcl-2*. Enhanced apoptosis was observed in prostate cancer cells with restored miR-205 (by means of treatment with cisplatin and doxorubicin) [66]. miR-574-3p controls *Bcl-xL* and substantially induces apoptosis in the prostate cancer cells. The expression of miR-574-3p in prostate cancer is decreased; however, genistein treatment up-regulated its expression [67].

The *Polycomb* group gene *Bmi-1* is overexpressed in prostate cancer stem cells; however, as was demonstrated previously, there was a decrease in *Bmi-1* expression in cells treated with NVP-LDE-225 (erismodegib). The inhibitory effect of erismodegib on *Bmi-1* expression is realized through up-regulation of miR-128. The introduction of antagomirs in the cells to knock down

miR-128 revealed that erismodegib-induced apoptosis was significantly disrupted [68].

MicroRNAs IN DIAGNOSTICS OF PROSTATE TUMORS

An important challenge for oncourologists at present is the development of an objective and highly sensitive method of diagnosing prostate cancer without invasive intervention, which not only causes discomfort to the patient but also is associated with the risk of serious side effects [64].

The role of microRNAs as potential clinical biomarkers of prostate cancer has been extensively investigated, since miRNA expression profiles in healthy and tumor tissues of prostate, and even between different types of prostate tumors, have been classified. MicroRNAs can easily be detected in a small sample volume by specific and sensitive methods, one of which is real-time quantitative real-time PCR (qRT-PCR). miRNA samples can be easily isolated from the majority of biological fluids, including serum, plasma, urine, saliva, breast milk, tears, and semen, where they are extremely stable [15, 69]. miRNAs are highly conserved between the species, allowing for preclinical studies in animal models. Furthermore, it was demonstrated that tumor cells released miRNAs into the bloodstream [70] and that the miRNA expression profiles in plasma/serum of the patients with cancer were different [15, 36]. Mitchell el al. [71] showed that the level of expression of serum miR-141 was considerably different in PC patients as compared with healthy controls.

Taylor and Gercel-Taylor [70] demonstrated in their studies the increased expression of miR-21, miR-141, miR-200, miR-200c, miR-200b, miR-203, miR-205, and miR-214 in circulating exosomes. Since the microRNA expression profile reflects the origin of the tumor and correlates with the development and progression of PC, the use of miRNAs is a promising approach for the diagnosis of disease with high specificity. To date, the exact miRNA expression profile that can differentiate between healthy individuals and PC patients is not established; however, research in this direction is underway, and some encouraging results have been obtained (Table 2) [7].

In 2006, Volinia et al. [41] examined the expression profiles of 228 miRNAs in 56 tumorous and seven normal tissues samples of the prostate and revealed overexpression of miR-106a in the tumor samples. Ambs et al. [72] revealed an increased expression of miR-32, miR-26a, miR-181a, miR-93, miR-196a, miR-25, miR-92, and let-7i in 71 samples of microdissected tissues, including 60 tumor samples and 16 normal tissue samples. Note that an increased expression of miR-101, miR-30c, and miR-195 was observed in patients with extraprostatic extension of the tumor, suggesting a possible role of these miRNAs in the prediction of the disease course. It is interesting that further studies demonstrated the carcinogenic role of miR-181a and miR-196 in the development of several cancers by regulating such fundamental processes of tumor development as epithelial-mesenchymal transition (EMT) [80] and invasive properties of the cells [81]. Porkka et al. [50] analyzed the miRNA expression profiles in 13 different tissue samples of PC patients, including four samples with the diagnosis of BPH, five samples with PC without prior hormonal therapy, and four samples with the hormone-refractory type of PC. It was demonstrated that the expression of 37 miRNAs (including miR-16, miR-99, let-7 family, and others) was decreased, while the expression of 14 miRNAs was increased. It is interesting that down-regulation of the expression level of miR-205, miR-100, and miR-30 family was observed only in the samples of PC resistant to hormone therapy, suggesting a possible role of these miRNAs for prediction of castration-resistant PC. The results of the study Porkka et al. are partly consistent with the data presented in the study of Ozen et al. [82], where the authors observed substantial down-regulation of the expression profile of 16 miRNAs in samples of PC tissues as compared to ten normal tissue samples. For instance, analysis of the expression profiles of 85 miRNAs showed that 76 of these were characterized by low expression with a tendency of a global down-regulation in the case of early PSA recurrence. Martens-Uzunova et al. [73] examined the expression of 102 miRNAs in the tissue samples with microarrays and found dysregulated expression profiles of 54 miRNAs, which could clearly distinguish PC from normal tissue samples. In addition, the expression of 25 miRNAs (13 of them had decreased and 12 had increased expression) statistically significantly correlated with the Gleason score, metastasis, and changes in the *ETV1* transcription factor gene [73]. Thirteen microRNA, which, according to [73], showed dysregulated expression, were specially examined by Larne et al. [74] in tissue samples from 49 patients with diagnosed prostate cancer and 25 men without PC by qRT-PCR. As a result of the analysis, seven miRNAs were identified (miR-96-5p, miR-183-5p, miR-183-3p, miR-145-5p, miR-205-5p, miR-221-5p, and miR-409-5p); they were differentially expressed in PC samples as compared to normal tissue. The highest level of expression up-regulation was observed for miR-96-5p and miR-183-5p, and the expression of miR-145-5p and miR-221-5p was down-regulated. These four miRNAs were combined for the analysis and, based on them, the miRNA index quota (miQ) was elaborated. With this index it is possible to distinguish between prostate tumor and normal tissue with great precision, as well as to predict the aggressiveness of the tumor and its metastatic status. The prognostic value of this index was further confirmed in four independent cohorts, and, despite the differences in their sizes, methodology and design of the research, the obtained results indicate that miQ can serve as a useful clinical biomarker [7].

Table 2. miRNAs with highest diagnostic value in prostate cancer

References	Sample type	Deregulated miRs (number of miRs)	miRs, selected as biomarkers	
[72]	60 microdissected cellular elements of tumor tissue and 16 samples of normal tissue	Upregulated (21), downregulated (21)	miR-32, miR-26a, miR-181a, miR-93, miR-196a, miR-25, miR-92, and let-7i	↑
[73]	102 prostate cancer samples and 102 normal tissue samples	Deregulated (54)	miR-205	↓
[74]	49 prostate cancer samples and 25 normal tissue samples	Deregulated (7)	miR-96-5p, miR-183-5p	↑
			miR-145-5, miR-221-5p	↓
[75]	Serum samples of PC patients ($n = 36$) and healthy donors ($n = 12$)	Upregulated (6), downregulated (4)	miR-20b, miR-874, miR-1274a, miR-1207-5p, miR-93, miR-106a	↑
			miR-223, miR-26b, miR-30c, miR-24	↓
[76]	Plasma samples of PC patients ($n = 78$) and healthy donors ($n = 28$); urine samples of PC patients ($n = 118$) and healthy donors ($n = 17$)	Deregulated (12)	miR-107, miR-574-3p	↑
[77]	40 prostate cancer samples and 40 corresponding normal tissue samples; urine samples of PC patients ($n = 36$) and of healthy donors ($n = 12$)	Downregulated (2)	miR-205, miR-214	↓
[78]	Urine samples of the patients with PC ($n = 8$), BPH ($n = 12$) and healthy donors ($n = 10$)	Deregulated (17) (only seven of them were chosen for further analysis)	miR-1825 (only in PC)	↑
			miR-484 (in PC and BPH)	↓
[79]	76 samples of PC and the corresponding adjacent normal tissue	Upregulated (5), downregulated (10)	miR-96, miR-182, miR-182*, miR-183, miR-375	↑
			miR-16, miR-31, miR-125b, miR-145, miR-149, miR-181b, miR-184, miR-205, miR-221, miR-222	↓

For Tables 2 and 3: PC, prostate cancer; BPH, benign prostatic hyperplasia; ↑, increased expression; ↓, decreased expression.

In recent years, the discovery of circulating miRNAs resulted in an active search for new biomarkers. In 2011, Moltzahn et al. [75] compared the levels of miRNA expression in the sera of 12 healthy men and 36 PC patients subdivided into groups with low, intermediate, and high risk of PC based on the CAPRA scores. The expression profiles of ten miRNAs between normal control and PC patient samples were considerably different. Moreover, in the patient group, the expression of four miRNAs (miR-223, miR-26b, miR-30, and miR-24) were down-regulated, and of six miRNAs (miR-20b, miR-874, miR-1274a, miR-1207-5p, miR-93, and miR-106a) were up-regulated. Two miRNAs showed a linear relationship between miRNA levels and cancer risk: miR-24 steadily decreased with risk, whereas miR-106a steadily increased with risk of the disease development. A similar analysis of miRNA expression was conducted by Bryant et al. in 2012 [76]. They examined the changes in miRNA expression profiles, comparing 78 plasma samples of PC patients and 28 plasma samples of healthy individuals with the use of a microarray analytical system for the performance of real-time PCR. A total of 12 miRNAs were found to have changed expression profiles, and the increased expression of miR-107 and miR-574-3p in patients with localized prostate cancer was confirmed. It should be noted that these two miRNAs were present in high concentrations in the urine of men with PC as compared with the control, suggesting the possibility of their use as noninvasive biomarkers. In 2013, Srivastava et al. [77] evaluated the expression of miR-205, miR-214, miR-221, and miR-99b in 36 PC patients and a control corresponding to the group of healthy men. It was demonstrated that miR-205 and miR-214 were considerably downregulated in the samples of PC patients as compared with control samples [77]. Quite recently, the urine samples of 30 individuals (eight patients with PC, 12 patients with BPH, and 10 healthy men) were

examined to determine the miRNA expression profiles [7]. Urine is an easily accessible source for molecular markers, so miRNA detection in the urine samples of the PC patients is an ideal noninvasive method of diagnosis [15, 36]. A total of seven differentially expressed miRNAs (miR-1234, miR-1238, miR-1913, miR-486-5p, miR-1825, miR-484, and miR-483-5p) were identified and chosen for further analysis. The latter revealed considerable changes in the expression patterns of two miRNAs, miR-1825 and miR-484, demonstrating high and low expression levels in PC samples as compared with healthy controls, respectively. The same tendency, however, was observed in BPH with respect to miR-484. The expression patterns of miR-1825 and miR-484 were not confirmed when the patients were reexamined two years later. At the same time, in summary of the data on miRNA dysregulation and PSA levels, the presence of prostate cancer was detected with 40% sensitivity and 81% specificity. These results indicate that biomarkers detectable in body fluids that are obtained noninvasively can be a good alternative for mass screening of the disease [7].

THE ROLE OF miRNA IN PREDICTING THE COURSE OF PC

At present, attempts to identify the prostate cancer risk group in which patients after radical prostatectomy will experience relapse with metastatic disease are based on the evaluation of a series of biological markers, including PSA, Gleason scores, and histology of the tumor. However, these markers cannot statistically significantly predict the clinical outcome for patients. It is therefore necessary to identify molecular markers of tumor aggressiveness [15].

Prostate cancer is characterized by an unpredictable clinical course. Some tumors remain latent for years, while others rapidly progress to metastatic diseases. While every third man at the of age 50 has a histologically confirmed diagnosis of PC, only 10% of the cases are diagnosed as a clinically meaningful type of the disease, implying that most PC cases do not progress to a level dangerous to human life. It is still unclear what factors contribute to the development of an aggressive type of PC, a metastasizing and possibly fatal disease. [36]. The identification of prognostic markers that can predict the course of the disease plays an important role in the choice of the therapeutic approach for the PC treatment. For instance, the optimal modality for the treatment of a clinically localized early stage of the disease is radical prostatectomy and radiation therapy, while the mainstay treatment of late PC is the removal of the testes (orchiectomy), which are the source of androgens. Orchiectomy reduces the symptoms of the disease by 70–80%, but in most cases the tumor recurs within two years to the incurable and castration-resistant stage, which finally leads to death from PC [83].

Androgen signaling is associated with the expression of miRNAs, as some of them have been shown to modulate the androgen pathway, which further facilitates the labeling of prostate carcinomas in accordance with resistance to castration [36]. For example, the expression of miR-125b [60], miR-21 [84], and miR-141 [17] is regulated by androgen-dependent element (ARE), which controls the activation of these miRNAs and thus the inhibition of its targets. miR-331-3p is also associated with the regulation of the androgen-receptor (AR) signaling pathway due to the overexpression of its own targets; *ERBB-2* gene expression is associated with the disease progression and the androgen-receptor (AR) signaling pathway [17, 36]. miR-141, miR-143, and miR-145 are involved in cell migration upon cancer development [12]. It was demonstrated that the down-regulation of miR-143 and miR-145 was associated with the PC progression [85] and the development of metastases [86]; it also correlated with the Gleason score [36]. To determine the markers of micrometastases development in PC, Brase et al. [87] conducted a comparative analysis of miRNA expression in serum samples from patients with localized and metastatic PC. It was demonstrated that the expression levels of 69 miRNAs were increased in patients with metastatic cancer. It was also found that the expression level of the three miRNAs, miR-141 [15, 87], miR-200b, and miR-375, increased with increasing tumor stage and Gleason score [64]. Bryant et al. [76] conducted a comparative analysis of miRNA expression in plasma samples of the patients with localized and metastatic PC. A total of 16 differentially expressed miRNAs that also included miR-141, miR-200b, and miR-375 were identified. The latter three miRNAs are important in relation to the PC progression and can potentially be used as a test system for the diagnosis and detection of patients with micrometastases [76]. In addition, Yaman Agaoglu et al. [88] showed that miR-141, miR-21, and miR-221 were characterized by increased expression levels in the plasma samples of patients with metastatic PC compared with the patients with localized PC.

The development of metastases in PC is also associated with down-regulation of miR-16, miR-34a, miR-126*, miR-205, mir-146a and up-regulation of miR-301 and miR-125b. miR-126* inhibits expression of the protein, which is often overexpressed in PC. It is known that miR-126, the sequence of which corresponds to alternative strand of miR-126*, is up-regulated in metastatic prostate cancer xenograft lines. It is possible that the mechanism of selection for the miRNA chain sequence may be involved in the development of metastases [89]. It is known that the expression of miR-203 gradually decreases in advanced forms of PC with metastases, suggesting possible relationships between its expression and antaganistic activity [90]. The expression of miR-146a is suppressed in tumors with metastases; this miRNA is involved in the formation of a premetastatic niche [91] and the development of castration-resistant prostate

cancer [92]. A correlation of some other miRNAs with the Gleason score (miR-1, miR-31, and miR-205), tumor stage (miR-125b, miR-205, and miR-222), perineural invasion (PNI)(miR-1, miR-10, miR-30c, miR-100, miR-125b, and miR-224), and biochemical progression (miR-96) was reported (Table 3) [36].

It was demonstrated that the miR-200 and miR-205 family controls EMT and is up-regulated in tumor tissues [12, 50], resulting in the suppression of a number of genes, including *SLUG*, *ErbB3*, *E2F1*, *E2F5*, and *ZEB2* [64]. EMT is a complex process in which epithelial cells acquire phenotypic characteristics of mesenchymal cells. This facilitates the process of increased cell motility and invasion, which are characteristic of metastasis [64]. During EMT cancer cells lose their ability to reverse transition into epithelial cells. This process is associated with a decrease in the expression of epithelial proteins, such as E-cadherin and transitive plaktoglobin, and an increase in the expression of mesenchymal markers, such as vimentin, fibronectin, and alpha-smooth muscle actin. These changes are also associated with an increased activity of matrix metalloproteinases (MMPs), such as MMP2, MMP3, MMP9, resulting in an invasive phenotype. All of the above processes lead to increased invasion and cell migration in many cancers, including PC [12].

It was demonstrated that miR-29b functioned as tumor suppressor during the development of metastatic PC. The expression of miR-29b suppresses unknown targets with further invasion and metastasis, and the gene for matrix metalloproteinase 2 (*MMP-2*) is the target of miR-29b [64, 103]. Overexpression of miR-29b in metastatic PC cells induced expression of E-cadherin, while the expression of mesenchymal markers, such as N-cadherin, Twist, and Snail, was down-regulated, suggesting complete cancellation of EMT with subsequent acquisition of less invasive phenotype [104].

It is interesting that some studies demonstrated a tumorigenic role of miR-181a and miR-196 in several types of cancer by regulating the basic processes of the malignant tumor development, such as EMP and invasive properties of the cells [6]. It was shown that the expression of miR-1 and miR-200 decreased with PC progression, and the mesenchymal marker Slug directly down-regulated these miRNAs. Overexpression of either miR-1 or miR-200 inhibits the development of EMT in humans and the mouse through the regulation of the mesenchymal marker Slug [64, 105]. Recent studies showed that the miR-200 family controlled the EMT process by influencing *ZEB1* and *ZEB2* gene expression [106].

About 50% of PC cases are characterized by the expression of the *TMPRSS2-ERG* fusion gene, although the clinical and pathological significance of this change is still unclear [36, 107]. There is evidence that the status of the fusion gene determines the prognosis of the disease, which may be considered in the treatment of PC patients. To date, the only known association between the *TMPRSS2-ERG* fusion gene and microRNA expression was described in a study of 170 patients who underwent radical prostatectomy. It was demonstrated that a low level of miR-221 expression was associated with the presence of the fusion gene and correlated with the development of metastases [108].

Thus, to date, a large body of data on microRNA expression profiles in PC has been accumulated. However, these data are often contradictory. The lack of consistency in the results of different studies may be due to different study design, differences in sampling methods, sample contamination, and the different sensitivity and specificity of the platforms used. A summary of miRNAs with the highest predictive value is given in Table 3.

FUNCTIONAL IMPORTANCE OF miRNAs FOR PC TREATMENT

Since it became known that miRNAs are involved in the process initiation, tumor progression, and metastasis, their targeted action is seen as a potentially effective method of cancer therapy [15, 36]. For several years, different approaches of modulating the functions of microRNAs have been developed. MicroRNAs that act as tumor suppressors typically have reduced expression in cancer and microRNAs acting as oncogenes are usually overexpressed. Therefore, restoring the function of miRNAs in the first case, or by inhibiting their expression in the second case, it is possible to obtain the new methods of treatment.

The expression of miR-141 and miR-375 is increased in circulating blood and prostate tumor tissue. Szczyrba et al. [109] showed that the functional target of miR-375 was the *SEC23a* tumor suppressor gene, and the targets of miR-141 from the miR-200 family are the genes for the *ZEB* family transcription factors that suppress EMT, the main component in the development of metastases [15, 110].

It is known that azobenzene, the simplest aromatic azo compound, blocks the function of miR-21, acting as a potential inhibitor of the miRNA expression [36, 111]. For this reason, the treatment of cancer based on the use of miRNAs as therapeutic agents implies the obtainment of promising results that will have an undoubted value in the future, although microRNA analysis of is still far from clinical use. Nevertheless, at present, the first phase of clinical trials on the antisense blocking of miR-122 in the liver of nonhuman primates was held. It resulted in a reduction of cholesterol synthesis and an improvement in the fatty acid metabolism [36, 112].

It was found that each type of cancer expressed its unique set of individual miRNAs that may change with the disease progression. For instance, it was demonstrated in PC tissues that miR-145, miR-34a, miR-205, miR-146a, miR-101, miR-449a, miR-200, and miR-330 were down-regulated, while miR-221/222, miR-21, miR-23, and miR-125b were up-

Table 3. miRNAs with highest prognostic value in prostate cancer

References	Sample type	Clinical parameters	Deregulated miRs (number of miRs)	miRs, selected as biomarkers
[73]	102 samples of prostate cancer and corresponding normal tissue	Biochemical recurrence	Upregulated (12),	miR-19a, miR-130a, miR-20a/106/93 ↑
			downregulated (13)	miR-27, miR-143, miR-221/222 ↓
[93]	40 tissue samples of patients after prostatectomy (20 without early biochemical recurrence and 20 with early biochemical recurrence)		Upregulated (2),	miR-135, miR-194 (40% of cases) ↑
			downregulated (4)	miR-145, miR-221, miR-222 ↓
[79]	76 samples of prostate cancer and corresponding normal tissue		Upregulated (5),	miR-96 ↑
			downregulated (10)	
[94]	149 prostate cancer samples and 30 samples of corresponding normal tissue		Upregulated (1)	miR-205 ↓
[95]	Tissue samples with biochemical recurrence and no signs of malignancy		Downregulated (2)	let-7b and let-7c ↓
[96]	21 tissue samples with biochemical recurrence and 28 normal tissue samples		Upregulated (4)	miR-100 ↑
[97]	82 prostate cancer samples (41 samples with biochemical recurrence and 41 samples of normal tissue)		Downregulated (3)	miR-1, miR-133b ↓
[98]	Blood serum samples of PC patients (eight with biochemical recurrence and eight normal)		Upregulated (3)	miR-194, miR-146-3p ↑
[99]	Plasma samples of PC patients ($n = 82$)	Castration resistance	Upregulated (2)	miR-21, miR-145 ↑
[100]	28 samples of localized PC, 14 samples of castration-resistant PC, and 12 tissue samples with BPH		Upregulated (4),	miR-32, miR-148a, miR-590-5p, miR-21 ↑
			downregulated (3)	miR-99a, miR-99b, miR-221 ↓

Table 3. (Contd.)

References	Sample type	Clinical parameters	Deregulated miRs (number of miRs)	miRs, selected as biomarkers
[86]	Six samples of primary-localized PC and seven samples of PC with bone metastases	Metastasis	Downregulated (5)	miR-508-5p, miR-143, miR-145, miR-33a, miR-100 ↓
[90]	36 PC samples, eight tumor samples of the patients with metastases, and eight normal tissue samples		Downregulated (1)	miR-203 ↓
[71]	Serum samples of PC patients with metastases ($n = 25$) and normal control ($n = 25$)		Deregulated (6)	miR-141 ↑
[87]	Serum samples of patients with localized ($n = 14$) and metastatic PC ($n = 7$)		Upregulated (5)	miR-141, miR-375 ↑
[76]	Serum samples of PC patients ($n = 72$), serum samples with metastatic PC ($n = 47$), plasma samples of PC patients ($n = 55$), and plasma samples with metastatic PC ($n = 24$)		Upregulated (2)	miR-141 and miR-375 ↑
[101]	Serum samples of patients with localized ($n = 58$) and castration-resistant ($n = 26$) PC	Castration resistance	Upregulated (3),	miR-141, miR-375, miR-378* ↑
			downregulated (1)	miR-409-3p ↓
[102]	Serum samples of patients with localized ($n = 20$), androgen-independent ($n = 20$), castration-resistant ($n = 10$) PC and BPH ($n = 6$)		Upregulated (1)	miR-21 ↑

regulated. Hence, the first are the suppressor, while the second are oncogenic miRNAs. Down-regulation of oncogenic miRNAs suppresses the growth of cancer cells and blocks the process of metastasis in PC. By reducing the level of expression of miR-221 and miR-222 in the androgen-independent LNCaP-Ab1 cell lines, the cellular response to the introduction of androgens in the cell medium was restored. The use of miR-221/222 plays important role in the treatment of castration-resistant PC [64, 113].

The ZEB2 transcriptional repressor is known as the EMT activator and can facilitate the development of metastases in some tumors. The product of *ZEB2* gene inhibits the transcription of miR-145, which is a strong inhibitor of the EMT process. In turn, *ZEB2* is the miR-145 target gene. The data obtained by D. Ren et al. [114] showed that down-regulation of *ZEB2* not only repressed invasion, migration, EMT, and the stemness of PC cells but also suppressed the capability of PC-3 cells to invade bone in vivo. It should be noted that the *ZEB2* expression level as revealed by immunohistochemical analysis was positively correlated to bone metastasis, the serum free and total PSA level, and the Gleason score in PC patients; it was also negatively correlated with miR-145 expression in PC tissue samples. These data suggest that a double-negative feedback loop between *ZEB2* and miR-145 contributes to PC progression and metastasis, and they have therapeutic relevance for the treatment of PC bone metastasis [114].

CONCLUSIONS

MicroRNAs are important molecules for understanding the mechanisms of the development of any tumor. According to the literature, there are more than 50 miRNAs known to date to be involved in the pathogenesis of PC. MicroRNAs, as key regulators of gene expression, can influence the biological properties of prostate cancer cells, such as cell proliferation, apoptosis, invasion ability, and metastasis. miRNAs also have an influence on the complex of proteins involved

in PC progression and are promising diagnostic and prognostic biomarkers that can be used in the clinic for PC treatment.

The use of microRNAs in the diagnosis of PC has great potential, primarily due to their relative stability and ease of detection. However, their use is limited at present by conflicting data obtained as a result of various studies because of the lack of standardized methodologies and reference genes for the data normalization. It is unlikely that any single microRNA will reach the required level of diagnostic and prognostic accuracy for use in clinics, because, as many studies have shown, up-regulation of specific miRNAs can be observed in various types of tumors. Given that miRNA expression patterns are specific to each type of cancer, it is hoped that there a test system for noninvasive early diagnosis of PC will be developed in the near future and will include analysis of the expression profiles of a number of miRNAs, as was done for pancreatic adenocarcinoma [115].

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