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REVIEWS

MicroRNAs AS PROMISING DIAGNOSTIC AND PROGNOSTIC MARKERS FOR THE HUMAN GENITOURINARY CANCER

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Genitourinary cancer (GUC) represents more than one fifth of all human cancers. This makes the development of approaches to its early diagnosis an important task of modern biomedicine. Circulating microRNAs, short (17–25 nucleotides) non-coding RNA molecules found in human biological fluids and performing a regulatory role in the cell, are considered as promising diagnostic and prognostic biomarkers of cancers, including GUC. In this review we have considered the current state of research aimed at assessing microRNAs as biomarkers of such human GUC types as malignant tumors of the bladder, kidney, prostate, testicles, ovaries, and cervix. A special attention has been paid to studies devoted to the identification of microRNAs in urine as a surrogate "liquid biopsy" that may provide the simplest and cheapest approach to mass non-invasive screening of human GUC. The use of microRNA panels instead of single types of microRNA generally leads to higher sensitivity and specificity of the developed diagnostic tests. However, to date, work on the microRNAs assessment as biomarkers of human GUC is still of a research nature, and the further introduction of diagnostic tests based on microRNAs into practice requires successful clinical trials.

Key words: cancer; human genitourinary system; microRNA; diagnostic markers

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INTRODUCTION

Genitourinary cancer (GUC), including urinary tract cancer and also cancers of the female and male reproductive systems, represents a high percentage of all malignant neoplasms [1–7], and its proportion in men and women is approximately the same [8]. Depending on a particular world region, the GUC contribution to the total number of human malignant diseases varies from 20% to 23% [9, 10]. The most common types of GUC include malignant tumors of the prostate, uterine body, kidney, cervix, bladder, and ovaries. For example, in the structure of cancer incidence in the Russian Federation, their proportions are respectively 5.1%, 3.8%, 2.8%, 2.6%, and 2.5% (https://spb.medsi.ru/articles/statistika-onkologicheskikh-zabolevaniy). The prostate cancer and cervical cancer are associated with the highest mortality rates [11]. A common feature of most genitourinary tumors detected at the stages of invasive or metastatic cancer is the absence of characteristic symptoms in the early stages of the disease [1, 3, 12, 13]. Diagnostics of GUC at the late stages of the disease progression significantly impairs the 5-year survival rates of patients [9]. The development of methods for diagnostics of malignant neoplasms at earlier stages has always been considered as one of the promising approaches to combating cancer, both in general and particularly in relation to human GUC [14, 15].

Modern diagnosis of GUC includes instrumental methods such as sonography, endoscopy, and pyelography, as well as more high-tech methods of computer, magnetic resonance, and positron emission tomography [16, 17]. Tissue biopsy remains a mandatory method of confirming the diagnosis in the case of GUC [18]. Also, in the diagnosis of these diseases, molecular genetic and biochemical methods are widely used; these include determination of various biomarkers, especially in relation to population screening for GUC [17–19]. In addition, biomarkers are used to assess the prognosis of GUC development and response to therapy [17].

The last decade is characterized by growing interest in microRNAs as potential diagnostic and prognostic biomarkers for GUC [20]. MicroRNAs, whose size ranges from 17 to 25 nucleotides (nt), belong to a special class of non-coding RNAs (ncRNAs). These microRNAs are involved in the regulation of various physiological processes and the progression of human diseases; they may act as both oncogenic factors and tumor suppressors as well [21–24]. To date, 2654 microRNA sequences are known in humans (http://www.mirbase.org, Release 22.1). Up to 400 different mRNAs may represent targets to a single microRNA, so it is estimated that between one third and half of human genes are directly regulated by microRNAs [25, 26]. The biological functions of individual microRNAs have been well studied using *in vivo* knockout models and transgenic overexpression experiments [27]. Their role in various biological functions such as cell differentiation, embryogenesis, organogenesis and apoptosis has been established [28, 29]. Since microRNAs play a significant role in cell proliferation and differentiation,

it is assumed that their dysfunctional expression can lead to a number of pathological processes, including neoplastic diseases [26, 30]. Although microRNAs are mainly localized intracellularly, some of them are found in the extracellular environment (including various biological fluids); these microRNAs found in biological body fluids are known as "circulating microRNAs" [31, 32]. These circulating microRNAs are considered as attractive candidates for minimally invasive and noninvasive biomarkers for diagnosing various types of cancer [32].

In this review we have considered the current state of research on the use of circulating microRNAs as diagnostic and prognostic biomarkers for such types of GUC as bladder cancer, kidney, prostate, testicular, ovarian, and cervical cancers. The introductory part briefly covers the biogenesis and detection methods of circulating microRNAs as potential biomarkers. Particular attention has been paid to studies devoted to the determination of microRNAs in urine as biomarkers of the so-called surrogate "liquid biopsy", which can reflect the pathophysiology of a human disease in real time and provide the simplest and cheapest approach to mass non-invasive screening of human GUC.

1. ORIGIN, BIOLOGICAL FUNCTIONS, AND METHODS FOR DETERMINATION OF microRNAs

1.1. MicroRNA Biogenesis

The canonical pathway of microRNA maturation begins in the cell nucleus with the transcription stage. Sequences encoding microRNAs are evolutionarily conserved and localized in various parts of the genome: introns, exons of protein-coding genes, intergenic regions [33]. In the human genome, microRNA loci are located in close proximity to each other, forming a polycistronic transcription unit [34]. The loci are transcribed by RNA polymerase II with the formation of primary microRNA (pri-microRNA), containing "hairpin" structures of RNA molecules several hundred nt long, "capped" and polyadenylated, respectively, at the 5′- and 3′-ends [33]. During the next stage, the pri-microRNA is cleaved by RNAse III Drosha with the formation of microRNA precursors (pre-microRNA), the RNA molecules of about 70 nt in size; their structure represents a "hairpin" bearing 2 nt overhang at the 3′ end (Fig. 1) [35]. Pre-microRNA is transported from the cell nucleus into the cytoplasm with the participation of the exportin-5 protein, where RNAse III Dicer "in collaboration" with TRBP (transactivation response RNA-binding protein) and Argonaute (AGO1–AGO4) proteins cuts out the loop region from it; this leads to the formation an asymmetric double-stranded RNA molecule 19–24 base pairs (bp) long with 2 nt overhangs at both 3′ ends (Fig. 1). At the final stage of microRNA maturation involving chaperone proteins (in particular, Hsc70 and Hsp90), microRNA binds to a protein of the Argonaute family (AGO1–AGO4) to form a riboprotein complex known as RISC (RNA-induced silencing complex). During complex formation the double-stranded molecule bends; this leads to its unwinding and one of the chains fits between the protein subunits ("guide") and remains intact, while the second ("passenger") is displaced and undergoes degradation [35]. Along with the canonical one, there are non-canonical pathways for microRNA maturation, which are divided into Drosha- and Dicer-independent [35]. In addition, the transport of pre-microRNA from the nucleus to the cytoplasm can be carried out by the exportin-1 protein, which also represents an important alternative pathway for microRNA processing [36].

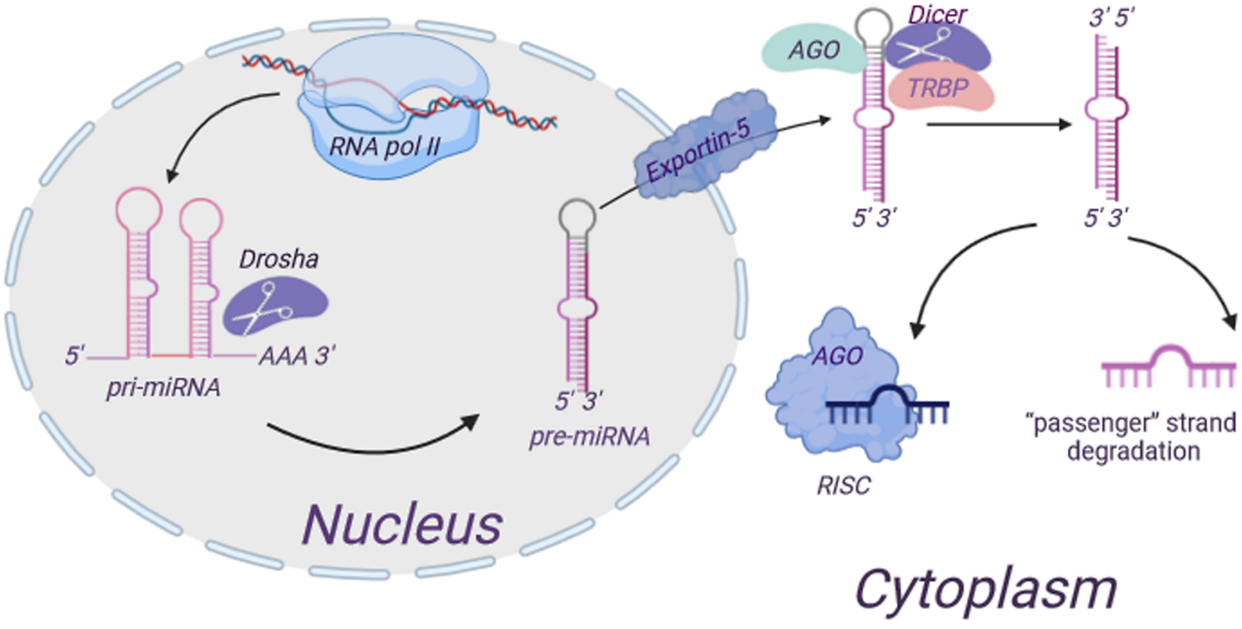

Figure 1. Schematic representation of the canonical pathway of microRNA maturation.

1.2. Regulatory Role of microRNAs

The mechanism of microRNA-mediated regulation of gene expression is based on repression of mRNA translation [26, 37]. It is believed that most often microRNA binds to the sequence of the 3′-untranslated region (3′-UTR) of mRNA; this binding involves nucleotides 2–7 or 2–8 of microRNA from the 5′ end (the so-called seed region), thereby blocking its translation and inducing deadenylation and decapping (Fig. 2) [38, 39]. A number of additional proteins, such as proteins of the GW182 family, are involved in the formation of the complete riboprotein gene shutdown complex, which performs the cleavage of mRNA by the RISC component AGO2 endonuclease, which initiates decapping of the mRNA by the DCP2 protein, followed by 5′-3′ degradation by exoribonuclease 1 (XRN1) [40]. In addition, microRNA binding sites have also been identified in other regions of the mRNA, particularly in the 5′-UTR and coding sequence [41].

1.3. Circulating microRNAs

Circulating microRNAs represent an insignificant part of all microRNAs, the main part of which is localized inside the cell, but they are present in detectable quantities in all body fluids, including blood and urine [41, 42]. The origin of circulating microRNAs can be associated both with their directed secretion into the intercellular space (as part of the process of intercellular interaction), and with cellular metabolism and cell death [43]. In both cases, microRNAs subsequently enter from the intercellular space into the biological fluid (for example, into the bloodstream). Many microRNAs are found in various types of biological fluids, but some show specific presence only in a limited number of types of fluids [42]. The resistance of microRNAs to the effects of ribonucleases present in biological fluids is due to the fact that microRNAs circulate as riboprotein complexes formed by RISC component proteins (primarily the Ago2 protein, with which up to 90% of microRNAs in blood plasma are associated), nucleophosmin, and high density lipoproteins [41, 44]. In addition, microRNAs circulate in biological fluids as components of extracellular vesicles: exosomes (30–100 nm in diameter), ectosomes (100–1000 nm in diameter), as well as apoptotic bodies [41, 42].

1.4. MicroRNA Detection Methods

MicroRNA was first detected in 1993 by means of Northern blotting [45], a method including electrophoretic separation of microRNA, followed by its transfer to a nitrocellulose membrane, and hybridization with (usually fluorescently) labeled DNA probes. Although this method of microRNA detection is still used, it has low sensitivity and is time- and labor-consuming [46, 47]. Today, for targeted detection of microRNAs, various versions of real-time polymerase chain reaction (RT-PCR) are widely used: with linear primers, stem-loop RT-PCR, two-tailed PCR-RT and ligation-RT-PCR (Fig. 3) [47]. The ligation-RT-PCR (Fig. 3D) avoids the reverse transcription step [48], which is usually characterized by low efficiency, thereby reducing the sensitivity of detection in general. The most commonly used method for microRNA detection is stem-loop RT-PCR (Fig. 3C). A hairpin primer provides a more than 100-fold improvement in detection sensitivity compared to linear primers [49]. The “two-tailed” RT-PCR method (Fig. 3B) has been developed to increase the specificity of microRNA detection: it uses a primer with a hairpin structure, the ends of which are complementary to the two terminal sequences of the analyzed microRNA [50]. The determination of microRNA can be carried out not only in the RT-PCR format, but also in the digital droplet PCR (ddPCR) format, which is generally accompanied by a decrease in the detection limit and an increase in its accuracy [51, 52].

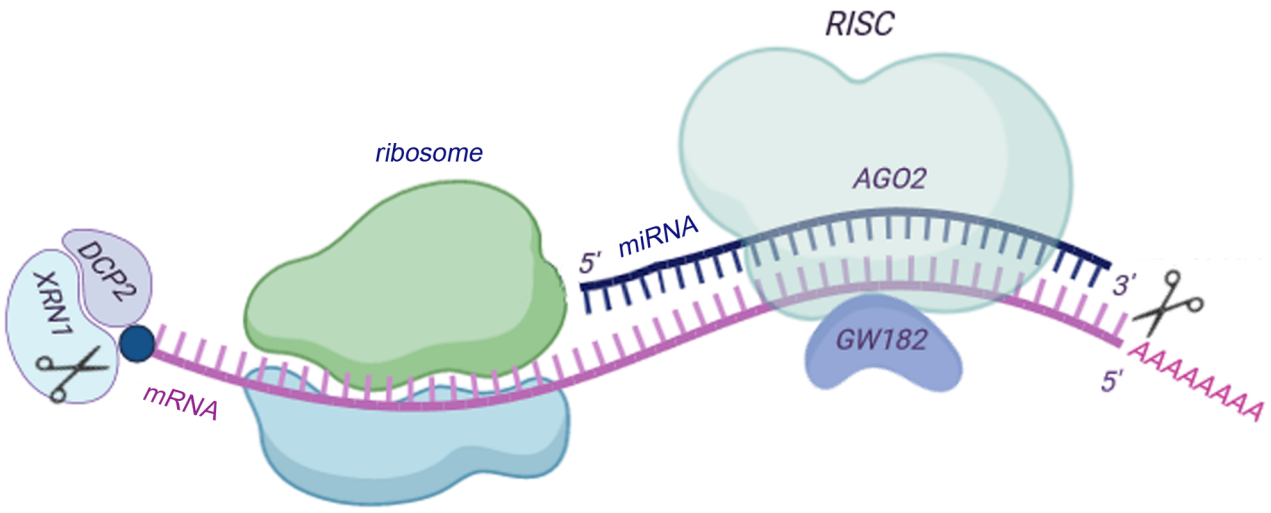

Figure 2. The role of microRNAs in the regulation of gene expression.

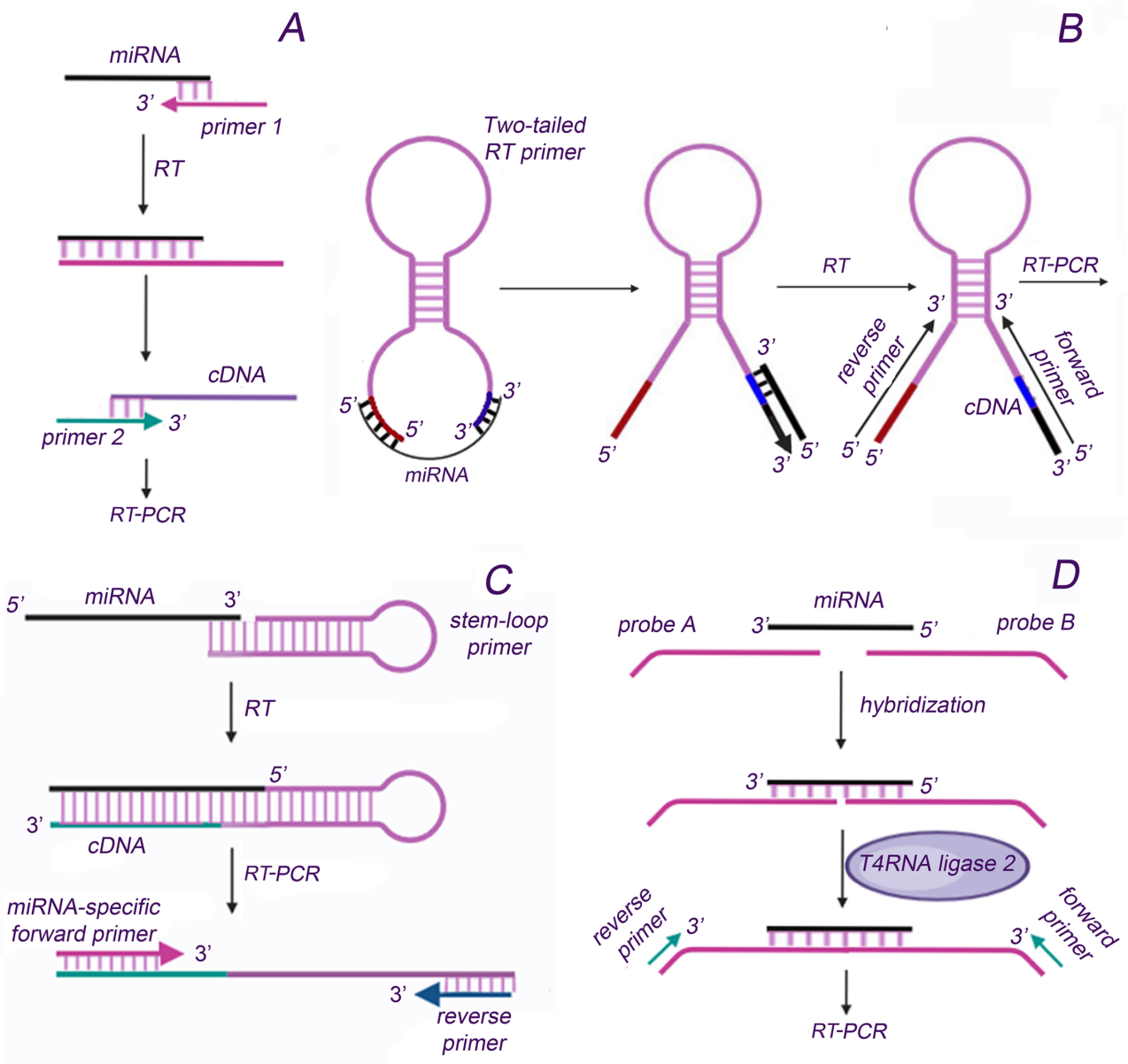

Figure 3. Schematic representation of RT-PCR variants of detection of microRNA molecules: RT-PCR with linear primers (**A**), two-tailed RT-PCR (**B**), stem-loop RT-PCR (**C**), ligation-RT-PCR (**D**).

Besides PCR, approaches based on the use of isothermal amplification methods, such as rolling-circle amplification, loop-mediated amplification, catalytic hairpin assembly, hybridization chain reaction, and a number of others have been proposed [46, 47]. It should also be noted that in recent years, an approach based on identifying microRNAs using CRISPR/Cas nucleases is actively developed [47]. However, to date, all these approaches have not become widespread and are basically not used in studies aimed at evaluating the diagnostic and prognostic significance of microRNAs as biomarkers of human diseases.

DNA microarrays and next generation sequencing (NGS) methods are widely used for microRNA profiling in the search for potential biomarkers of human diseases [53]. The advantages of microarrays include the ability of simultaneous analysis of hundreds of microRNAs. However, the sensitivity and selectivity of detection are low, and the dynamic range does not exceed three orders of magnitude [46, 47, 53]. A number of technological improvements (enzymatic elongation of microRNA sequences, the use of additional fluorescently labeled probes that are ligated with microRNA during hybridization on immobilized probes, the use of probes with a hairpin structure and LNA (Locked Nucleic Acid) probes) make it possible to increase the sensitivity and selectivity of microRNA determination, but with a significant increase in the cost of analysis [46, 53]. In contrast to DNA microarrays, which use known microRNA

sequences, the NGS method allows not only to perform the quantitative determination of known microRNAs with high sensitivity and in a wide dynamic range, but also to detect previously unknown microRNAs [47]. Being a rather expensive method, NGS is currently becoming increasingly popular for determination of the microRNA profile in various human pathologies [47, 53].

2. MicroRNA IN MALIGNANT TUMORS OF THE HUMAN GENITOURINARY SYSTEM

In subsequent chapters of this review we will use the generally accepted standardized naming system for microRNAs, having the form hsa-miR-(N)-3/5p [54]. The designation begins with an indication of the microRNA species (hsa — *Homo sapiens*), which will be omitted in the context of this review. The next letter block indicates a mature single-stranded microRNA (miR), followed by a number (N) assigned during annotation (for example, miR-19), which may be followed by a Latin letter (a, b, c, etc.), used to indicate the close relationship of miRNA sequences (for example, the sequences of mature miR-19a and miR-19b differ by only one base). The number is followed by an indicator of the hairpin precursor strand, from which the microRNA originates (3p for 3′, 5p for 5′).

2.1. Bladder Cancer

Bladder cancer is the tenth most common cancer worldwide with high morbidity and mortality rates [55]. Bladder tumors are divided into two types: low-grade, non-muscle-invasive, and high-grade, muscle-invasive tumors. Until now, the gold standard for its diagnosis is cystoscopy, a highly invasive procedure that can give false-negative results in the case of carcinoma *in situ* [56, 57]. Besides cystoscopy, additional methods are used for accurate diagnosis of bladder cancer: X-ray analysis and computed tomography [57, 58]. There are various treatments for bladder cancer (surgery, chemotherapy, radiation therapy), but prognosis and clinical response vary between patients, and the relapse rate and threat of disease progression persist over the next 5 years [59].

Good evidence now exists that ncRNAs, particularly microRNAs, are associated with the occurrence and development of bladder cancer [60–62]. At the same time, there is a change in the expression profile of microRNAs both in tissue samples and in the profile of microRNAs in the blood and urine of patients with bladder cancer [63-65]. Sequencing of tissue samples from patients diagnosed with bladder cancer revealed 74 microRNAs; 33 microRNAs were characterized by increased expression, and 41 demonstrated decreased expression as compared to healthy donors [64]. More than 50 microRNAs were found in the urine of patients with bladder cancer, their expression was either increased or decreased compared to the healthy controls [66]. For example, in the urine of patients, a decrease in the levels of miR-99a, miR-125b, miR-30b, miR-204, miR-532-3p, and miR-10a was observed [67–69], while the levels of miR-126, let-7b-5p, miR-149-5p, miR-146a-5p, and miR-423-5p increased compared to normal levels [66]. Similar results were also obtained for a number of other microRNAs: miR-3-5p, miR-19-5p, and miR-93-5p [70].

The level of certain microRNAs in the urine of patients can serve not only as a diagnostic sign of bladder cancer, but also can help in determining the type of bladder cancer, the degree of its malignancy and the prognosis of the development of this disease. For example, the level of miR-200c decreased in non-muscle invasive bladder cancer [71]; the levels of miR-618 and miR-125b-5p increase in muscle invasive bladder cancer [72]; the level of miR-146a-5p increased significantly in high-grade bladder cancer [73]; the level of miR-10a correlated with the degree and stage of bladder cancer [69]; high levels of miR-149-5p and miR-93a-5p were associated with poor overall survival of patients [66].

Determination of microRNAs in urine of patients is the most informative diagnostic approach for bladder cancer, and comparative analysis of several miRNAs shows higher diagnostic efficiency [74]. For example, analysis of miR-96-5p and miR-183-5p abundance in urine, the sensitivity for diagnosing bladder cancer reached 88.2%, and the specificity of 87.8% were significantly higher than in the of each miRNA analyzed separately [75]. Determining the ratio of the abundance of miR-126 (increased in bladder cancer) and miR-152 (decreased in bladder cancer) in the urine of patients made it possible to diagnose bladder cancer with a specificity of 82% and sensitivity of 72% [76]. Recently, a correlation was shown between the levels of miR-106b-3p (reduced in bladder cancer), miR-199a-5p and miR-145-3p (overexpressed in bladder cancer); this increased the sensitivity of bladder cancer diagnostics [77]. Analysis of the presence of certain microRNAs in urine, and especially determination of the microRNAs in each particular case, is a promising diagnostic approach for bladder cancer especially in context of tumor type determination, and disease course prediction [74].

2.2. Kidney Cancer

Renal cell carcinoma (RCC) is the 15th most common type of cancer in the adult population, accounting for about 3% of malignant neoplasms [78, 79]. Its distinctive feature is resistance to chemotherapy [79, 80]. The main types of RCC include: clear cell carcinoma (ccRCC), papillary renal cell carcinoma (pRCC), chromophobe carcinoma (chRCC), and oncocytoma. RCC accounts for approximately 90% of all renal malignancies [81, 82]. The main methods of treatment for RCC include chemotherapy, radiation therapy and surgical resection, while their disadvantages include difficulties in detecting small tumors, resistance to chemotherapy and subsequent relapses

of the disease [82]. At the time of diagnosis of RCC, 18% of patients already had metastases, and 20–50% of patients subsequently developed metastases after either partial or radical nephrectomy [83–85]. Currently, there are no reliable methods for predicting metastases in RCC. The search for sensitive, minimally invasive biomarkers that would help to diagnose RCC at an early stage, as well as to predict tumor metastasis, occurs in various directions, including analysis of microRNA abundance in the blood and urine of patients [79, 86].

More than 60 microRNAs have been detected in the blood serum and urine of RCC patients; their abundance significantly differed from the norm (in 30% of cases it reduced, and in 70% it increased) [86]. Interestingly, the pattern of urinary microRNAs with altered abundance differed from the serum pattern of such microRNAs. At the same time, about 20 microRNAs with altered abundance (in most cases it increased) were found in the urine. A decrease expression was observed for several microRNAs classified as tumor suppressors (miR-126-3p, miR-30c-5p, miR-328-3p, and miR-15a) [86]. In addition, miR-15a can be considered as a potential diagnostic marker for all types of RCC, thus differentiating malignant and benign kidney tumors with a specificity of 98.1% and a sensitivity of 100% [80].

Some microRNAs have been proposed, as promising candidates for the role of biomarkers of the most common type of kidney cancer, ccRCC; the level of their abundance was either significantly increased compared to the norm (miR-122, miR-1271, miR-15b, and miR-210 [87, 88]), or decreased (e.g., miR-30a-5p [89]). miR-498, miR-183, miR-205, and miR-31 have been proposed as markers for the development of renal oncocytoma [90]. Since their urinary level increases as the tumor develops, so they are considered as preoperative biomarkers diagnosing the disease at an early stage.

The abundance level of some microRNAs may be used for detection of progressive forms of RCC, as well for prediction of patient survival and clinical response to therapy. For example, in the case of a progressive form of ccRCC, the presence of miR-328-3p in the urine is significantly reduced, and the abundance level correlates with the overall survival of patients: patients with a high level of miR-328-3p abundance demonstrated longer survival as compared to patients who had low abundance of miR-328-3p (and lower survival). This makes miR-328-3p a promising candidate for prognostic biomarkers of ccRCC [91].

miR-191-5p, miR-324-3p, and miR-186-5p, are potential markers of the development of metastases in RCC; their abundance is significantly increased in urine of patients with metastatic ccRCC [92]. It is proposed to use miR-210-3p as a biomarker to assess the clinical results of treatment in patients with metastatic ccRCC; the level of its abundance in urine correlated with the response to therapy [93]. In the non-metastatic form of RCC, the presence of microRNAs of the miR-let-7 family (let-7a, let-7b, let-7c, let-7d, let-7e, and let-7g) was significantly increased in the urine of patients. The most promising biomarker candidate is miR-let-7a, which allows diagnosing this form of ccRCC with a specificity of 81% and a sensitivity of 71% [94].

2.3. Prostate Cancer

Prostate cancer (PCa) is the most commonly diagnosed malignancy and the second leading cause of cancer mortality among men [95]. Early diagnostics is important because localized PCa can be cured with radical prostatectomy or radiation therapy, whereas metastatic prostate cancer is incurable. Currently, the most widely used approach to detect PCa is a blood test to assess the rise in prostate specific antigen (PSA), which plays an important role in the early detection of PCa [96]. However, its level can also increase in benign prostatic hyperplasia (BPH), as well as in acute prostatitis [97]. The low specificity of PSA for the diagnostics of PCa requires a highly invasive procedure, prostate biopsy, to make an accurate diagnosis through histopathological tissue analysis.

Currently, 449 microRNAs have been found in the urine of PCa patients; 301 miRNAs were characterized by decreased abundance and 148 miRNAs had increased abundance compared to samples obtained from healthy donors [98]. At the same time, analysis of their abundance in patients before and after prostatectomy showed significant differences for 89 microRNAs: 49 microRNAs had increased abundance, and 40 had decreased abundance. Also, in urine samples obtained from patients after surgery, the abundance level of 25 microRNAs was significantly reduced compared to the norm [98].

Changes in the abundance of a number of urinary microRNAs can serve as an indicator of the early stage of PCa. For example, miR-320a is considered as a marker for early diagnostics of PCa; its level was greatly reduced in the early stages of the disease [99]. In addition, a combined analysis of the abundance of two microRNAs, miR-205 and miR-214, made it possible to diagnose PCa with a sensitivity of 89% and a specificity of 80% (the level of both microRNAs was significantly reduced in PCa patients) [100]. Urinary microRNA levels may also indicate the type of cancer and serve as a prognostic marker. For example, in the metastatic type of PCa, an increased abundance of miR-107 and miR-574-3p was observed compared to the norm [101]. Another study [102] showed association between increased levels of miR-21 and decreased levels of miR-200c with metastatic PCa. In addition, a panel of 7 microRNAs (miR-3195, miR-let-7b-5p, miR-144-3p, miR-451a, miR-148a-3p, miR-512-5p, and miR-431-5p),

which are functionally associated with cancer aggressiveness, has been proposed for prognosis of PCa aggressiveness [103].

Certain attempts have been undertaken to investigate whether the presence of certain microRNAs in urine can be used to differentiate between PCa and BPH. However, it has not yet been possible to identify microRNAs whose levels in urine would be used for such differentiation with both sufficiently high sensitivity and specificity. For example, an increased level of miR-1825 allowed differentiating between PCa and BPH with a sensitivity of 60% and a specificity of 69%, and miR-484 with a sensitivity of 80% but a specificity of only 19% [104]. Also, for diagnostic purposes, it was proposed to use the ratio of miR-1913 and miR-3659 abundance; its value was significantly higher in PCa than in BPH (sensitivity 75.0%; specificity 78.6%) [105].

Profiling of 92 miRNAs in urine has shown that in PCa, the abundance of 14 miRNAs was significantly increased, and 30 miRNAs were significantly decreased compared to BPH [106]. Based on the data obtained, diagnostic and prognostic panels were proposed, based on the analysis of the ratios of the abundance of several microRNAs. For example, a panel based on determining the level of 3 microRNAs — miR-222-3p, miR-24-3p (increased in PCa), and miR-30c-5p (decreased in PCa) could differentiate PCa from BPH. The panel, including the analysis of the ratio of the abundance of miR-125b-5p, miR-let-7a-5p, and miR-151-5p, has been proposed as a prognostic panel that would subdivide patients into high and low risk groups after radical prostatectomy in order to make decisions about further treatment regardless of the results of clinicopathological examination [106]. For more reliably prediction of the risk of relapse after prostatectomy, a diagnostic panel was developed based on determining the levels of 5 microRNAs in urine (miR-151a-5p, miR-204-5p, miR-222-3p, miR-23b-3p, miR-331-3p) in combination with the PSA test [107].

2.4. Testicular Cancer

Testicular germ cell tumors (TGCTs) are the most common malignancies among young men aged 20 to 40 years [108]. According to the 2022 WHO classification, there are two subgroups of TGCTs: pure seminomas and non-seminomas. Although teratomas, the histologic subtype of nonseminoma, are benign tumors, they are genetically unstable, unpredictable in biological behavior, and resistant to chemotherapy. Teratomas have the potential for rapid growth, leading to the development of somatic malignancy of a non-germ cell tumor [109]. Survival rates for TGCTs vary depending on several factors. These include the stage of the cancer, age, and overall health of the person. The overall 5-year survival rate for TGCT is 95%. In modern clinical practice, surgical treatment with post-chemotherapy retroperitoneal lymphadenectomy (pcRPLND) is often used [110]. Tests for alpha-fetoprotein (AFP), β-subunit of human chorionic gonadotropin (βhCG), and lactate dehydrogenase (LDH) are recommended as diagnostic markers. However, these markers have limited sensitivity (<60%) [111]. Thus, at present there is a clear need for new minimally invasive diagnostic biomarkers of TGCTs; they may help to clarify the clinical stage of the disease and to reasonably select individual treatment tactics for the patient. Identification of specific microRNAs in biological fluids of TGCT patients is one of the strategies used to find such markers.

Currently, the main studies aimed at detecting microRNAs associated with the TGCT development are carried out on of tumor tissues and serum samples. Four microRNAs significantly increased in serum samples from TGCT patients (miR-371a-3p, miR-372-3p, miR-373-3p, and miR-367-3p) were found to be the most promising diagnostic markers [112]. The best results were obtained for miR-371a-3p; using the miR-371a-3p level it was possible to diagnose TGCT with a specificity of 96.1% and a sensitivity of 91.8% [113]. Moreover, miR-371a-3p abundance correlated with clinical stage, primary tumor size, and response to treatment. This miRNA also appears to be a sensitive marker of relapse and response to chemotherapy, providing an additional criterion for selecting patients for surgical lymphadenectomy [114, 115]. For the differential diagnosis of TGCT subtypes, miR-375-3p and miR-375-5p were proposed; their overexpression was associated with the development of teratomas, processes of necrosis/fibrosis, as well as tumor viability [111, 116]. However, it should be noted, that their reliability as diagnostic markers has not been proven. Regarding the study of microRNA as a biomarker in urine samples from TGCT patients, we were unable to find publications reporting the results of such studies (or that they were currently conducted).

2.5. Ovarian Cancer

Ovarian cancer (OC) is the fifth most common form of malignancy in women worldwide [117]. Epithelial ovarian cancer (EOC) is the most prevalent type of ovarian tumor, which accounts for about 85% of all cases. The main histological subtypes of EOC include serous, endometrioid, clear cell, and mucinous EOC [118]. The serous subtype of EOC is diagnosed in 25% of cases [119]. Difficulties in OC detection at an early stage, as well as resistance to chemotherapy, make it the most lethal malignant gynecological disease [120]. More than 70% of OC cases are diagnosed in late, incurable stages (III and IV) [121]. OC diagnostics currently involves blood levels of biomarkers such as serum cancer antigen 125 (CA-125) and human epididymal protein 4 (HE4) [122]. Currently, the preferred method for initial evaluation of suspected

cases is a combination of CA-125 testing and transvaginal ultrasound; however, it does not have sufficient reliability for differentiating benign from malignant tumors [123, 124]. Thus, OC detection at an early, curable stage requires more reliable screening tools that could improve patient stratification and determine treatment tactics.

Currently, microRNAs circulating in the biological fluids of patients, such as blood, saliva, ascites, fallopian tube liquid, and urine are considered promising diagnostic biomarkers of OC. The urine is a better source of microRNA, since it is formed near the affected organ and its collection is non-invasive [125, 126]. Urinary microRNA profiling has shown that in OC, an aberrant abundance was observed for more than 60 microRNAs, and in the vast majority their abundance level was reduced compared to the norm [127]. A comparative analysis of the abundance of 18 microRNAs in the urine of OC patients and healthy women showed that the most significant changes in the level of representation were observed for four microRNAs: in two of them the levels increased (miR-92a and miR-200b), and in the other two they decreased (miR-106b and miR-100) [128]. The authors of the study suggested that miR-92a, miR-200b, miR-106b, and miR-100 could be considered as promising candidates for the role of diagnostic markers of OC [128]. Also, miR-15a and miR-let-7a were proposed as potential biomarkers of OC; they were characterized by significant changes in the levels of their presence in urine compared to the norm (the level of miR-15a increased, and miR-let-7a decreased) [127].

In the serous ovarian cancer (SOC) a change in the abundance of 38 microRNAs was observed in the urine of patients, but only one microRNA, miR-30a-5p, had increased (more than twofold) abundance, while the abundance of the remaining 37 microRNAs was reduced [129]. The level of miR-30a-5p was higher at stages I-II of the disease than at stages III-IV, as well as in cases of well or moderately differentiated forms of EOC, in contrast to poorly differentiated forms of SOC. In addition, the preoperative level of miR-30a-5p in urine was significantly higher than the postoperative level. This indicates that the tumor is the source of miR-30a-5p in the urine. Due to the fact that the abundance of miR-30a-5p was increased in the early stages of the disease, it was proposed as a biomarker for a screening test for SOC [129].

2.6. Cervical Cancer

Cervical cancer is the fourth most common cancer among women and the fourth leading cause of death from gynecological cancer [117]. The standard treatment for local cervical cancer includes radiation therapy in combination with chemotherapy using platinum-based drugs [130, 131]. However, more than 50% of patients develop resistance to therapy [132]. The main cause of cervical cancer is persistent infection of the cervix with oncogenic human papillomavirus, leading to intraepithelial lesions, histologically defined as lesions of cervical intraepithelial neoplasia [133]. Currently, squamous cell carcinoma antigen (SCC-Ag) is used as a biochemical marker for cervical cancer, which is associated with relapse and survival in squamous cell carcinoma of the cervix [134]. However, this biomarker has low selectivity: increased levels of SCC-Ag are also observed in serum of patients with head and neck cancer [135], oral cavity cancer [136], and lung cancer [137].

Currently, the search for new diagnostic markers for cervical cancer is aimed at detecting differentially expressed circulating microRNAs in samples of biological fluids, including blood (serum/plasma) and urine of patients. Most studies have focused on identifying diagnostic biomarkers in blood. In the serum of patients with cervical cancer changes in the abundance of 33 microRNAs were found as compared to the normal values: 17 microRNAs demonstrated increased abundance and 16 had decreased abundance [138]. 3 miRNAs with increased abundance (miR-9, miR-192, and miR-21-5p) had the highest specificity rates (up to 98%) for the diagnostics of cervical cancer. Based on this study, diagnostic panels combining several miRNAs have been proposed. These include miR-497, miR-16-2, miR-195, and miR-2861; miR-9, miR-192, and miR-205; miR-638, miR-203a-3p, miR-1914-5p, and miR-521; miR-21-5p, miR-199a-5p, miR-155-5p, miR-34a-5p, and miR-218-5p. It should be noted that microRNAs combined into a panel could have either a decreased or increased abundance in cervical cancer [138].

miRNA profiling in the urine of patients with cervical cancer resulted in detection of 6 promising miRNAs. Their abundance levels correlated with those in tissue biopsy samples, in scrapings from the cervix and in the serum of patients with a precancerous condition and cervical cancer [139]. The abundance of three microRNAs, miR-21-5p, miR-199a-5p, and miR-155-5p (onco-microRNA), in precancerous conditions and cervical cancer was significantly higher than in the control group of healthy women. On the contrary, the abundance of miR-145, miR-34a, and miR-218 (tumor suppressors) in precancerous conditions and cervical cancer was reduced, and their lowest levels were observed in the urine of patients (compared to serum and scrapings from the cervix). A combined analysis of miR-145-5p, miR-218-5p, and miR-34a-5p showed 100% sensitivity and 92.8% specificity and was proposed as a promising test for the differential diagnostics of patients with a precancerous condition and cervical cancer. It is suggested that a diagnostic model based on a panel including 3 miRNAs with increased abundance and 3 miRNAs with decreased abundance can provide more accurate information for the diagnostics and prognosis of cervical cancer [139].

CONCLUSIONS

To date, a significant volume of experimental results, convincingly indicating the potential of circulating microRNAs as promising diagnostic and prognostic markers of human GUC has been accumulated. For various types of GUC (bladder, kidney, prostate, ovarian, and cervical cancer), microRNA as a biomarker can be detected in urine; this creates the basis for the development of diagnostic approaches for non-invasive screening of various population groups with the aim of identifying these types of GUC in the early stages. The use of miRNA panels instead of single types of miRNAs generally leads to higher sensitivity and specificity for the diagnostic tests being developed. However, further implementation of such tests in practice requires successful clinical trials. From a technical point of view, their implementation is not difficult, since RT-PCR, the most common approach for quantitative detection of microRNAs, is widely used in routine practice of clinical diagnostic laboratories.

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COMPLIANCE WITH ETHICAL STANDARDS

This article does not contain any research involving humans or the use of animals as objects.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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МикроРНК КАК ПЕРСПЕКТИВНЫЕ ДИАГНОСТИЧЕСКИЕ И ПРОГНОСТИЧЕСКИЕ МАРКЕРЫ РАКА МОЧЕПОЛОВОЙ СИСТЕМЫ ЧЕЛОВЕКА

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Рак мочеполовой системы (РМПС) занимает значительную долю (более одной пятой) в структуре онкологических заболеваний человека, что делает разработку подходов к его ранней диагностике важной задачей современной биомедицины. Перспективными диагностическими и прогностическими биомаркерами онкозаболеваний, в том числе РМПС, служат циркулирующие микроРНК. Эти обнаруживаемые в биологических жидкостях человека короткие (17–25 нуклеотидов) молекулы некодирующей РНК выполняют в клетках регуляторную роль. В обзоре рассмотрено современное состояние исследований по оценке микроРНК как биомаркеров таких типов РМПС человека, как злокачественные опухоли мочевого пузыря, почки, предстательной железы, яичек, яичников и шейки матки. Особое внимание уделено исследованиям, посвящённым определению микроРНК в моче как суррогатной “жидкой биопсии”, которая может обеспечивать наиболее простой и дешёвый подход к массовому неинвазивному скринингу РМПС человека. Использование панелей микроРНК вместо единичных типов микроРНК в целом приводит к более высоким значениям чувствительности и специфичности разрабатываемых диагностических тестов. Однако к настоящему времени работы по оценке микроРНК как биомаркеров РМПС человека носят исследовательский характер и дальнейшее внедрение диагностических тестов на основе микроРНК в практику требует проведения успешных клинических испытаний.

Полный текст статьи на русском языке доступен на сайте журнала (http://pbmc.ibmc.msk.ru).

Ключевые слова: рак; мочеполовая система человека; микроРНК; диагностические маркеры

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