

Review article

MicroRNA: Potential Biomarkers in Chronic Kidney Disease

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SUMMARY

Introduction. Standard biomarkers for the diagnosis and follow-up of chronic kidney disease patients are appropriate neither in early diagnostics, adequate follow-up and progression assessment nor in complication development risk assessment. For that reason, a search for new, more suitable biomarkers continues. Various studies suggested microRNAs as a potential solution, as they are involved in the pathogenesis of diabetic nephropathy, kidney cancer and kidney function impairment in general.

Methods. Internet search engines were used to find and select relevant literature data and electronic databases.

Results. Research published so far, in oncology especially, have reported various single microRNAs and panels of microRNAs as candidates for routine diagnostic implementation. Chronic kidney disease is, however, quite complex in terms of etiology of the disease occurrence, since there are many causes that can lead to kidney tissue damage and impairment of its function and finally full development of the chronic kidney disease. MicroRNAs are stable in bodily fluids, and hemodialysis procedure does not affect their levels. Also, high RNase activity in chronic kidney disease patients does not accelerate microRNA degradation in their samples.

Conclusions. Literature data suggest that microRNAs are appropriate candidates for diagnostic use in chronic kidney disease. However, there are challenges that are yet to be overcome in order to use microRNAs routinely.

Keywords: microRNA, chronic kidney disease, hemodialysis

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INTRODUCTION

Chronic kidney disease (CKD) can be defined as an injury of the kidney tissue or its impaired function, lasting for three months or more, consecutively (1). According to the 2017 data, the disease prevalence is estimated to be around 9% of the population, where 0.07% is diagnosed with the stage V, and 0.04% is undergoing dialysis treatment (2). Treatment and care for these patients is a major financial burden to the health system. Even though the cost of treatment in the moderate stages of CKD is higher than the hemodialysis itself (3), these patients may develop a lot of different complications, cardiovascular in particular, which can gradually increase the cost of healthcare for a single patient (4). Also, the hospitalization rate is about 1.4 times higher in CKD patients compared to the rest of the population, with cardiovascular complications and bacterial infections being the most common causes (5, 6).

Cardiovascular disease is the leading cause of death in dialysis patients, with mortality being 10 - 20 times higher compared to the rest of the population (6, 7).

Standard biomarkers of diagnosis and follow-up of CKD patients are neither appropriate in early diagnostics, adequate follow-up and progression assessment nor in complication development risk assessment. For that reason, a search for new, more suitable biomarkers for CKD continues (8).

Various studies suggested microRNAs (miRNA) as a potential solution, as they are involved in the pathogenesis of diabetic nephropathy, kidney cancer and kidney function impairment in general (9 - 11).

Apart from their role in the disease development process, the biochemical properties of miRNAs qualify them for use as biomarkers. MiRNAs are produced in the cell and afterward packed into vesicles, which can circulate in bodily fluids. This is the main reason of these RNAs' relative resistance to the action of RNases, which are highly active in both blood and urine. Therefore, it is not too difficult to isolate and identify miRNAs in bodily fluids (12). Also, studies have demonstrated that dialysis of high RNase activity does not affect the results obtained from measuring the expression of miRNAs in these patients' samples (13, 14). MiRNAs are tissue-specific, meaning that a tissue miRNA profile can be established and used as a

marker tool for the diagnosis or progression assessment of a certain disease.

MicroRNA

MiRNAs are single-stranded non-coding RNA sequences, containing approximately 22 nucleotides. They were first encountered in the 90' and so far around 2000 human miRNAs have been identified (miRBase Database 22.1) (15, 16).

The primary miRNA transcript (pri-miRNA) is around 1000 nucleotides long and organized as a series of hairpin structures. Next, the Drosha enzyme, as a part of the microprocessor complex, is bound to the pri-miRNA hairpin and cuts off the individual hairpins. Both of these actions occur in the nucleus. Afterward, this precursor miRNA (pre-miRNA), 60 - 100 nucleotides long, is transported into the cytoplasm, where a Dicer enzyme cuts it in two, leaving a double-stranded miRNA duplex (17).

It is commonly believed that only one of the RNA chains of the duplex is active in gene expression control. The mechanism most frequently described is the formation of the RNA induced silencing complex (RISC), where the active/leading chain is included and therefore marked as „miR“. The complementary chain of the duplex is referred to as a minor or the follower miRNA and marked as „miR*“. Earlier findings suggested that the minor chain is being completely decomposed after the leading chain separates and forms the RISC, however, newer research showed that minor miRNA also contributes to the gene expression regulation. Since these conclusions are published, nomenclature had to be changed into miR-5p and 3p, instead of miR and miR*. Traditionally, what used to be marked as a leading, miR chain is now referred to as miR-5p, whereas the follower miR* chain is marked as miR-3p (Figure 1) (18).

After the Dicer's action and the formation of duplex RNA, it is bound to the Argonaut (AGO) protein into the RISC precursor complex. Next, the follower chain leaves the complex, and the leading chain remains attached and participates in regulation, more specifically, silencing the expression of the particular genes (19).

In addition to this canonical mechanism of miRNA synthesis and action, there are several other unconventional Drosha-independent pathways (such as mirtron, snoRNA, shRNA) and Dicer

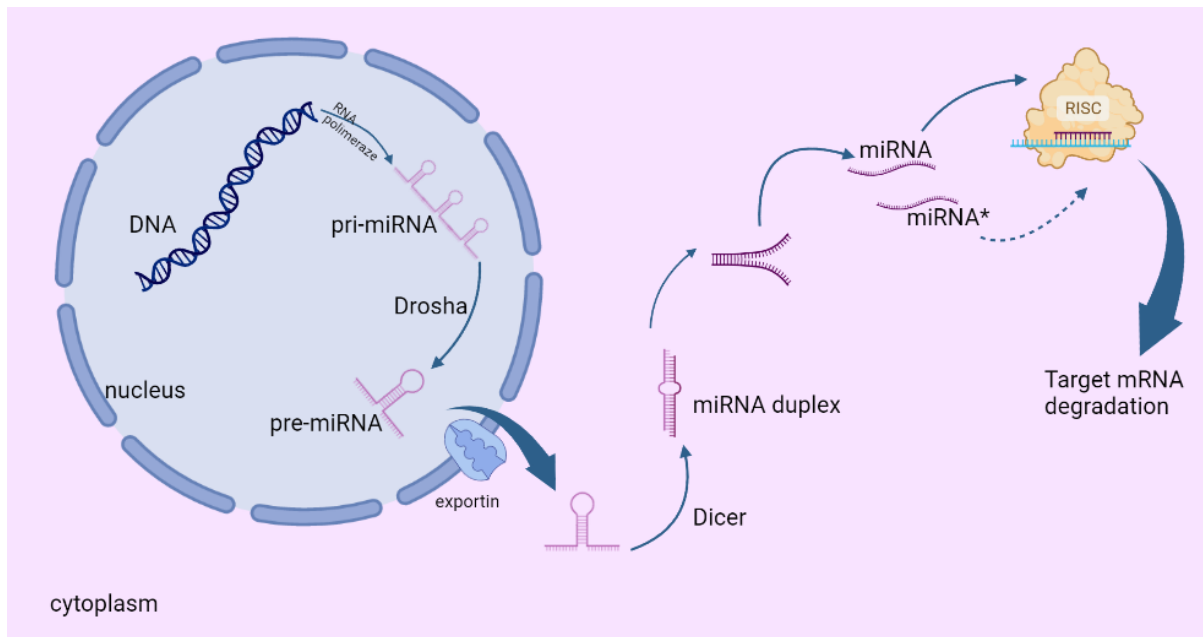


Figure 1. *MiRNA and RISC complex formation process*

Figure 1. Additional explanation. Up to the point of pre-miRNA formation, the processes of RNA polymerase and Drosha enzyme take place in the nucleus. Afterwards, pre-miRNA is being transported into cytoplasm by a specific exportin protein. In the cytoplasm, Dicer enzyme continues the processing and forms miRNA duplex that is later to be divided into two miRNAs, and one of them is to form the RISC complex and be involved into mRNA regulation and degradation.

independent pathways, when AGO serves as a tool for both transportation and duplex formation (with the help of action of tRNaseZ) (20).

Regulation of gene expression by RISC occurs at the mRNA level, by miRNA binding to the complementary 3' end of the non-coding part of the mRNA. In animals, the seed region for binding is usually nucleotides 2 - 8 of the 5' end of the mRNA. Perfect or near-perfect complementarity will lead to the complete degradation of the respective mRNA, while partial complementarity and binding will only inhibit the translation process without the mRNA degradation. In any case scenario, the mRNA will not work properly, the protein synthesis will be diminished and the expression of some genes therefore altered. Expression regulation can also be achieved by binding to the 5' end of the non/coding part of the mRNA, in terms of silencing or enhancing expression. Some miRNAs can regulate the expression of other small RNA types (21).

miRNA IN DIAGNOSTICS

Being secreted into extracellular vesicles or bound to the AGO proteins, miRNAs are excep-

tionally stable in bodily fluids (22). Serum, urine, and other body fluid samples could be as helpful as tissue biopsy samples if they were isolated and measured properly (23).

Current research, particularly in oncology, has identified various separate and panels of miRNAs as candidates for routine diagnostic implementation (23 – 25). The case of CKD is, however, quite complex in terms of etiology of the disease, since there are many causes of the kidney tissue damage and impairment of its function and finally full development of CKD (1).

Diabetic nephropathy is considered the most common cause of CKD (2) causing the loss of kidney function in around 40% of diabetic patients (26). Microalbuminuria, which is a golden standard in diabetic nephropathy diagnostics, is faulty in terms of specificity and sensitivity. Microalbuminuria is present in cases of cardiovascular disease, diabetes, inflammation and hypertension (27). MiRNAs are directly involved in the processes of translation control of appropriate mRNAs, which is why they could serve as biomarkers. Used as part of the defined miRNA panels, they were able to distinguish between different nephropathies and their causes

and complications. Some miRNAs are differently expressed in serum/plasma and urine. MiRNA-124 is lower, whereas 21, 192, 195 and 451 are higher in expression in plasma. In urine, miR-195 and 451 are low, and 21, 124 and 192 are highly expressed. This miRNA profile of plasma and urine is reported in patients of the third grade of CKD (28). The production of cytokines involved in the kidney inflammation, such as the family of nuclear transcription factors (NR4A) and transforming growth factor beta, is also regulated by miRNA. Thus, miR-17-5p and miR-20a should be considered as possible biomarkers for monitoring the signaling pathways previously mentioned (29, 30).

Tissue fibrosis occurs in the final stages of kidney disease and causes progressive loss of kidney function (31). In this process, when extracellular matrix is reinforced and scar tissue is formed, TGF-beta plays a key role. TGF-beta is also a potential target for miR-328 (32). MiR-196a and b are expressed dominantly in the kidney and act as fibrosis inhibitors and therefore protect the kidney (33). Angiotensin II is considered to be an initiator of fibrosis. However, a study conducted on an animal model did not succeed in proving the link between angiotensin II and miR-184, which also contributes to fibrosis process (34). Another research, that used a culture of rat fibroblasts demonstrated that angiotensin II activates the expression of miR-184 (35).

MiR-21

MiR-21 belongs to the micro RNA 17 - 92 cluster, responsible for mitosis control and apoptosis inhibition (36). Some miRNAs from this cluster have been shown to be less expressed in CKD patients (37), whose kidney function declines partly due to increased apoptosis. MiR-21 expression is increased in various kidney diseases, and in experimental animals treated with miR-21 inhibitors, kidney function improves compared to untreated experimental groups (38, 39). Its expression is also high in vascular cells: smooth muscle cells, endothelial cells, as well as in myocardial cells and myofibroblasts (40). This miRNA is most likely active in the early stages of atherosclerosis, when its profibrotic effect seems to be useful to keep the newly formed plaque stable (asymptomatic plaque) (41). However, in the later stages, its pro-inflammatory effect plays a significant role in the formation of neointimal lesions and the overall effect is atherogenic (42). MiR-21 is also in-

creased in hypertensive patients with asymptomatic atherosclerosis. Research conducted with a patients with type 2 diabetes mellitus showed that this miRNA negatively affects kidney function (28). MiR-21 is also associated with the metabolism of xenobiotics and may affect the effectiveness of some drugs used for the treatment of these patients (43).

MiR-21 correlated negatively with mean diastolic blood pressure during 24 hours and positively with systolic and diastolic blood pressure, CRP and carotid intimal thickening. It is also positively correlated with left ventricular mass index. (44)

Animal models of hypertension, spontaneously hypertensive rats, showed an increase in mitochondrial reactive oxygen species (ROS), which may be the result of reduced expression of cytochrome b, encoded by mitochondrial genes (45). Recently published data showed that miR-21 has the ability to translocate from the cytosol to the mitochondria, affecting the mentioned gene and lowering its down regulation. Thus, it was concluded that miR-21 acts in compensatory mechanisms of blood pressure lowering and makes myocardial hypertrophy more mild in spontaneously hypertensive rats (45).

Most miRNAs have a lower expression in the plasma of CKD patients (miR-21 is one of the rarely high expressed ones) (46). The exact way this occurs is not fully explained, since normal activity of both Drosha and Dicer enzymes, which participate in the miRNA production is demonstrated. Whether or not there is increased miRNA degradation in these patients is still uncertain, however recent studies deny this. A study investigating the effect of hemodialysis on circulating miRNA levels concluded that this type of therapy had no effect on the change in miRNA concentration. The stability of miRNAs in body fluids can be explained by their secretion into extracellular vesicles and apoptotic bodies and binding to protein-miRNA complexes (12).

CHALLENGES IN DIAGNOSTIC IMPLEMENTATION OF miRNAs

The most suitable miRNA candidates for diagnostic implementation are usually identified in carefully planned research. To plan this type of a research, it is advised to use the following algorithm:

Step 1. Define the desired phenotype – pathological process we wish to examine.

Step 2. Screen to identify miRNA candidates for a distinguished effect on the examined process (microarray or RNA-seq).

Step 3. Confirm the screening results using another method (RT-qPCR, Northern blot, *in situ hybridization*)

Step 4. Find a connection between the obtained miRNA results and the appropriate genes (47).

After identification of a single or a group of miRNAs that would suit the experiment, the exact pathway of miRNA action can be investigated using a controlled cell culture or an animal model of the disease. The next step would be to further examine the expression levels in the human tissue samples and finally conclude whether or not the investigated miRNA can really be a potentially useful biomarker.

Unfortunately, most of the studies investigating miRNA are limited in terms of the number of subjects included, most often due to various financial reasons, therefore, it is difficult to translate the studies from fundamental to clinical practice.

Methods of isolation and expression measurement of miRNA should be also improved. To begin with, miRNA isolation should include as many of their sources in bodily fluids as possible, such as extracellular vesicles, apoptotic bodies and AGO protein complexes. Additionally, a universal assay control has not yet been established. The influence of personal factors, such as age, gender and applied treatment, to the miRNA presence in the sample should be investigated further and defined more precisely (48).

The MiRNA is quite stable and resistant to the RNase activity, meaning their half-life is quite long. Complexity of their synthesis and mechanism of action suggests that the use of artificial intelligence and bioinformatics will be required in order to track the expression control pathways of certain proteins, which are targets to appropriate miRNAs.

There was a dilemma if the process of hemodialysis can alter the miRNA's levels in the plasma samples. However, the studies that compared the samples before and after the treatment concluded that dialysis process does not affect the results of determining miRNA in samples of dialysis patients (13).

CONCLUSIONS

According to the results of the studies published so far, miRNA is suggested to be the appropriate candidate for diagnostic use in chronic kidney disease. The stability in bodily fluids and the interaction with the messenger RNA as a mechanism of gene expression control qualifies miRNA as potentially useful diagnostic marker of kidney diseases. However, there are challenges that are yet to be overcome in order to use the microRNA regularly, such as improvements in methodology, determination of a single or panels of miRNA that could be used and possible correlations with other clinically determined measurements.

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Mikro RNK: potencijalni biomarkeri kod hronične bolesti bubrega

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SAŽETAK

Uvod. Standardni biomarkeri za dijagnozu i praćenje hronične bolesti bubrega nisu u potpunosti adekvatni ni u ranoj dijagnozi, adekvatnom praćenju i proceni progresije, a ni u proceni rizika od razvoja komplikacija. Iz tog razloga, potraga za novim, pogodnijim biomarkerima je stalna. Mnogo studija preporučuje mikro RNK kao potencijalno rešenje, s obzirom na to da su uključene u patogenezu dijabetesne nefropatije, tumora bubrega i poremećaja funkcije bubrega uopšte.

Metode. Korišćeni su internet pretraživači za selekciju adekvatne literature i podataka, kao i elektronskih baza podataka.

Rezultati. Istraživanja publikovana do sada, naročito u oblasti onkologije, navode različite pojedinačne i panele mikro RNK kao kandidate za uvođenje u rutinsku dijagnostiku. Hronična bolest bubrega je, naime, prilično kompleksna u smislu etiologije pojave bolesti, s obzirom da mnogo različitih uzroka može dovesti do oštećenja bubrežnog tkiva i poremećaja bubrežne funkcije i, konačno, do potpunog razvoja hronične bubrežne bolesti. Mikro RNK su stabilne u telesnim tečnostima i proces hemodijalize ne utiče na njihov nivo. Takođe, visoka aktivnost RNaza kod bolesnika sa hroničnom bubrežnom bolešću ne ubrzava degradaciju mikro RNK u njihovim uzorcima.

Zaključak. Podaci iz literature ukazuju na to da bi mikro RNK mogle da budu pogodni kandidati za dijagnostičku primenu u hroničnoj bolesti bubrega. Ipak, i dalje postoje izazovi koji moraju biti prevaziđeni za uvođenje mikro RNK u rutinsku upotrebu.

Ključne reči: mikro RNK, hronična bolest bubrega, hemodijaliza