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Perspectives of application of microRNA as a biomarker for assessing the quality of kidney and liver transplants

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Abstract

Introduction. *Donor organ quality is critical for maintaining current and long-term graft function. More effective and diagnostically relevant tools for assessing the quality of a donor organ under transplantation will help optimize post-transplant monitoring, select appropriate clinical management strategies, and increase graft survival. MiRNAs can be used as such tools for early, non-invasive diagnosis of donor organ viability. Circulating miRNAs are found in various biological fluids; they are relatively stable and tissue-specific. Furthermore, precise laboratory methods for analyzing the expression of specific miRNAs are now available.*

Objective. *The aim of the review is to identify the prognostic value of microRNA in kidney or liver transplant recipients for the analysis of the donor organ status in the pre-transplant period.*

Material and methods. *This paper presents the results of studies identifying specific microRNAs for assessing donor organ quality. To analyze and structurize the literature, we searched the electronic databases MIRBase, PubMed, MedLine, eLIBRARY, and Google Scholar for the period from 1995 to 2025. This review includes 60 publications from Russian and international sources.*

Conclusion. *Current scientific data confirm the feasibility and potential of using microRNAs as biomarkers. Further research is needed to develop and optimize a diagnostic algorithm for organ transplantation.*

Keywords: microRNA, organ quality, kidney and liver transplantation

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CKD, chronic kidney disease

miRNA, microRNA

Introduction

Transplantation is the most effective method of replacement therapy, allowing clinicians to significantly improve the quality of life of patients with end-stage chronic kidney disease (CKD) or save the lives of patients with cardiac, hepatic or pulmonary failure. The shortage of donor organs still remains the main problem limiting the availability of transplant care for the population [1]. The use of expanded criteria donors and asystolic donors in clinical practice seems to be one of the ways to solve this problem [2, 3]. However, grafts obtained from expanded criteria donors are significantly more susceptible to ischemia-reperfusion

injury, as a result of which in the post-transplant period, the delayed graft function, graft dysfunction, rejection crises develop more often, and the graft survival time is also reduced [4–6]. Consequently, there is an urgent need to assess the quality of the allograft before transplantation in order to predict the surgery outcome.

There are two methods for preserving a donor organ from the moment of its explanting until transplantation: simple cold storage and machine perfusion [7]. However, for the restoration and maintenance of the viability of organs obtained from suboptimal donors, the use of machine perfusion would be preferable [8–10]. In turn, the perfusate can serve as a valuable material for assessing the donor organ quality. This material can be obtained non-invasively for further assays and reflect the condition of the entire organ, rather than the material from a separate area selectively obtained during biopsy. In addition, the perfusate reflects the quality of the organ even before transplantation; the results of the study are not affected by manipulations during surgery and in the postoperative period [11, 12]. Studies have been published demonstrating the possibility of using perfusate to predict a liver graft dysfunction by measuring the concentration of hyaluronic acid and aminotransferases [13–15]. Experiments have been conducted to identify markers of graft damage in the perfusate, in particular proinflammatory cytokines and growth factors, during hypothermic machine perfusion of the liver graft [16, 17]. However, all of these markers proved insufficiently informative for predictive diagnosis of liver graft damage. Furthermore, renal blood flow velocity and vascular resistance are assessed during hypothermic machine perfusion to determine the renal graft viability. A number of biochemical markers are also used to assess ischemic graft damage; however, the predictive ability of these markers has not been proven and is controversial [18–20].

Possibilities of using microRNA in kidney transplantation

Currently, there is particular interest in the use of miRNA as non-invasive markers in solid organ transplantation to assess the course of the post-transplant period, the effectiveness of immunosuppressive therapy, and to predict the risk of rejection [21, 22].

MiRNAs are a class of small endogenous noncoding RNAs, 19–25 nucleotides in length, which are involved in post-transcriptional regulation of gene expression in all eukaryotes [23, 24]. To date, over 28,000 miRNAs have been identified, of which more than 2,500 have been detected in humans [25]. MiRNA expression plays an important role in a variety of biological processes, such as the cell differentiation, apoptosis, and proliferation [26, 27]. MiRNAs suppress gene expression through complementary or partially complementary binding to its mRNA, resulting in inhibition of translation and destruction of target transcripts [28, 29]. MiRNA molecules are found in a stable state in many body tissues and are involved in the pathogenesis of a number of pathological processes, particularly in kidney transplantation [30].

Existing data indicate the presence of organ-specific miRNAs. Thus, Y. Sun et al. identified five miRNAs: miRNA-192, miRNA-194, miRNA-204, miRNA-215 and miRNA-216a, mainly expressed in kidney tissues [31]. The existence of kidney tissue-specific expression of miRNA-146a, miRNA-886, miRNA-192, miRNA-194, miRNA -204, miRNA-215, miRNA-216, miRNA-196a/b, miRNA-10a/b, miRNA-130, miRNA-146, miRNA-200a, miRNA-30a-e, miRNA-872 and miRNA-21 has been reported [32-34]. A number of studies have demonstrated the critical importance of the TGF- β1-associated signaling pathway in the development of rejection in the post-transplant period and the subsequent formation of sclerotic changes in transplant tissues [35–37]. In their studes, J. Wilfingseder et al., Z. Xu et al. and D. Joshi et al. reported the

role of miRNA-548d, miRNA-203, and miRNA-146a as regulators of the transcription factor SMAD 4, which initiates TGF-β1-induced transcription. In addition, miRNA-21 has a key effect on the development of TGF-β1-induced prosclerotic changes [38, 39]. Russian scientists discovered a clear relationship between the miRNA-21 expression level and the severity of kidney damage [40].

Prospects for the microRNA use as a biomarker for assessing the quality of liver graft

It is known that the impairment of graft function and the survival time of the donor organ are largely associated with the quality of the transplanted organ. The leading pathogenetic mechanism is ischemia-reperfusion injury of the graft [41]. Ischemia-reperfusion injury increases the immunogenicity of the donor organ, while the risk of rejection crises and graft dysfunction increases, and the length of the transplanted organ function decreases [42, 43]. Contemporary experimental and clinical studies show the potential of using organ-specific miRNA markers in the diagnosis of ischemia-reperfusion injury of the graft [44]. More efficient and accurate methods for determining the quality of donor organs will help avoid transplantation of non-viable organs, optimize immunosuppression, and reduce the risk of complications in the post-transplant period. Available data have demonstrated that miRNA profiling analysis in perfusate is more prognostically significant than directly in liver tissue [45, 46]. Within the framework of the study, the perfusion solution and liver graft biopsies from heart-beating and asystolic donors were collected at the end of the cold ischemia period. The levels of hepatocyte-specific miRNAs (miRNA-122 and miRNA-148a) and cholangiocyte-specific miRNAs (miRNA-30e, miRNA-222, and miRNA-296) in perfusate samples and biopsies were analyzed using

real-time polymerase chain reaction (PCR). The miRNA expression in the perfusate was found to be depended on the donor type (heart-beating donor and asystolic donor) and increased with increasing cold ischemia time and increasing serum gamma-glutamyl transferase levels. The level of miRNA-122 was higher in perfusates from the grafts with ischemic biliary tract injuries. The levels of cholangiocyte-specific miRNAs were significantly lower in similar perfusates. Thus, an increase in the ratio of hepatocyte-specific miRNAs to cholangiocyte-specific miRNAs may indicate the risk of developing ischemic biliary tract injuries [47].

The early liver graft dysfunction is associated with low organ viability after machine perfusion and directly affects transplant outcome. Therefore, there is an urgent need to find reliable biomarkers to assess organ quality and viability before transplantation. Previous studies have reported the use of perfusates to predict graft survival and prevent liver graft dysfunction by measuring lactate dehydrogenase, alanine aminotransferase, and alanine aminotransferase levels [48, 49]. A study was conducted to determine the prognostic value of analyzing miRNA levels in perfusate for the diagnosis of early liver graft dysfunction. The researchers found elevated levels of hepatocyte-specific miRNA-122 and an increased ratio of hepatocyte-specific miRNA-122 to cholangiocyte-specific miRNA-222 in the perfusate of liver grafts from asystolic donors and liver grafts with early graft dysfunction. Moreover, an increase in the ratio of hepatocyte-specific miRNA-122 to cholangiocyte-specific miRNA-222 correlated with the level of serum transaminases on the first day after transplantation. Long-term survival of the liver graft was significantly reduced with an increase in the ratio of miRNA-122 to miRNA-222 concentration in the perfusate. Moreover, the levels of miRNA-122 in the liver biopsy did not depend on the condition of the organ before transplantation and in the post-transplant period [50].

The possibility of using microRNA to assess kidney graft quality

A study of perfusate from kidney grafts obtained from expanded criteria donors demonstrated the value of perfusate as a valuable source for determining miRNA expression to assess graft viability in the pretransplant period. Thus, 10 miRNAs associated with the development of the delayed graft function were identified: miRNA-486-5p, miRNA-18a, miRNA-20a, miRNA-363-3p, miRNA -144-3p, miRNA -454-3p, miRNA-223-3p, miRNA-142-5p, miRNA-502-3p, miRNA-144-5p [51]. A subsequent study of kidney graft perfusate from expanded criteria donors 60 minutes after the start of hypothermic machine perfusion showed a statistically significant correlation between miRNA-21 expression and glomerular filtration rate at 6 and 12 months after transplantation, allowing for the prediction of organ function in the post-transplant period even before transplantation [52].

MiRNA levels in recipient urine can also be assessed as markers of graft integrity for post-transplant monitoring. MiRNA can enter the urine either from renal tissue cells or from cells infiltrating the renal tissue. MiRNAs are quite stable in urine [53]. The stability of their concentrations is explained by the fact that miRNAs form a complex with Ago 2 proteins, lipoprotein complexes, or can be contained in the membranes of extracellular vesicles [54, 55]. In particular, it was shown that the level of miRNA-146a in urine 10 days after transplantation significantly increased in kidney recipients from donors with ischemia-reperfusion injury [56].

In post-transplant monitoring, it is important to differentiate between the onset of acute cellular and humoral rejection, which is the main cause of graft loss. A group of scientists studied the potential of using miRNA to predict the development of acute rejection and the graft

survival. An association was found between a cellular rejection and changes in the content of a number of miRNAs in the urine; meanwhile, the miRNA-10a level was increasing, while the levels of miRNA-10b and miRNA-210 were decreasing in patients with a T-cell rejection. The level of miRNA-210 inversely correlated with the severity of the process and normalized after anti-crisis therapy [57]. Another study also showed a significant decrease in the concentration of miRNA-210 in the urine of recipients with a proven T-cell rejection [58]. Another group of researchers found different levels of a number of specific miRNAs in the graft tissues and in urine of patients with chronic transplant nephropathy with interstitial fibrosis and tubular atrophy compared to an intact graft. Moreover, the levels of miRNA-142-3p, miRNA-204, and miRNA-211 differed significantly among these groups of patients in the graft tissue and urine samples [59].

A delayed graft function is a common complication in the postoperative period, directly related to the condition of the transplanted organ. It has been established that by analyzing a panel of specific miRNAs in urine, it is possible to assess the graft function after surgery. The authors identified a panel of 6 miRNAs (miRNA-9, miRNA-10a, miRNA-21, miRNA-29a, miRNA-221 and miRNA-429), which is used to diagnose kidney damage [60].

Conclusion

Thus, current data on the key role of microRNAs in physiological and pathophysiological processes, as well as differences in the microRNA expression levels specific to certain tissues and organs, demonstrate the potential for using microRNAs as early, noninvasive molecular genetic markers for accurate and adequate assessment of donor organ quality and prognosis of transplant outcome. Perfusate, a valuable source of

biomarkers that allows for a reliable assessment of donor organ status in the pre-transplant period, can be used as the study material.

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