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EPIGENETICS IN CLINICAL TRANSPLANTOLOGY: DIAGNOSTIC, PREDICTIVE, AND THERAPEUTIC SIGNIFICANCE OF MICRORNA MOLECULES (SYSTEMATIC REVIEW)

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Epigenetics is the study of changes in gene expression that occur without alterations in the primary DNA sequence. These changes are mediated by chemical modifications of DNA, histones, and non-coding RNAs, collectively forming the epigenome, that determines the functional activity of the genome. Epigenetic mechanisms play a fundamental role in cellular differentiation, organismal development, and adaptation to external conditions. In medicine, they have attracted considerable attention due to their involvement in the pathogenesis of oncological, autoimmune, and neurodegenerative diseases. MicroRNAs (miRNAs), as key components of epigenetic mechanisms, play a critical role in controlling immune responses, including those occurring after organ transplantation. This has opened new opportunities for a personalized approach to the management of transplant recipients. Accumulating evidence on the role of miRNAs in solid organ transplantation suggests that integration of omics technologies may expand the existing arsenal of diagnostic criteria, serving as an auxiliary diagnostic tool for monitoring graft function. This systematic review presents a comprehensive analysis of the current literature on the clinical significance of miRNAs in modern transplantology. It highlights the diagnostic and predictive potential of specific miRNAs in relation to the development of complications in recipients of heart, lung, kidney, and liver transplants, and examines current approaches to the use of miRNAs as therapeutic targets.

Keywords: solid organ transplantation, miRNAs, diagnosis, prognosis, biomarkers, dysfunction, rejection, fibrosis.

INTRODUCTION

Organ transplantation is a definitive and highly effective treatment for end-stage diseases. However, despite continuous advances in surgical techniques and immunosuppressive therapies, the risk of post-transplant complications that require timely adjustments to treatment, persists [1]. Therefore, the development of new effective approaches aimed at improving long-term graft survival continues to be a key priority in transplant medicine.

For many years, biopsy – despite its inherent risks as an invasive procedure – has remained the gold standard for diagnosing graft pathology. In this context, increasing attention is being directed toward the development of minimally invasive diagnostic approaches. In particular, the identification and monitoring of circulating biomarkers in blood or other biological fluids represent a promising strategy for the early detection of graft dysfunction and the prevention of graft loss [2].

The advent of genomic and post-genomic technologies has represented a major breakthrough in the diagnosis and management of cardiovascular, oncological, and other severe diseases. Current research efforts are increasingly focused on elucidating the molecular mechanisms underlying the induction of immunological tolerance, as well as on identifying new diagnostic and prognostic markers for risk stratification [3]. In transplant medicine, particular importance is placed on understanding the regulation of innate and adaptive immune responses and exploring the potential for targeted modulation of gene expression.

A rapidly evolving area within this field is epigenetics – a branch of genetics that investigates changes in gene activity that occur without alterations in the primary DNA sequence [4]. The growing number of studies dedicated to the role of epigenetic mechanisms in disease pathogenesis highlights the increasing interest of both researchers and clinicians in this promising area.

A class of small non-coding RNAs (microRNAs or miRNAs) – has attracted considerable attention as key regulators of gene expression and as promising biomarkers and therapeutic targets for a range of socially significant diseases [5]. Since the discovery of miRNA molecules in 1993 by American geneticists Victor Ambros and Gary Ruvkun, numerous research has been conducted to elucidate their biological functions. To date, more than two thousand miRNAs have been identified in the human

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genome. The scientists, who revealed a new, fundamental principle of gene regulation, were awarded the 2024 Nobel Prize in Physiology or Medicine.

Given their central role in regulating cellular processes, microRNAs hold substantial potential for application across various fields of medicine, including transplantology, and are likely to remain a major focus of research in the coming years. However, the few systematic reviews on microRNAs in solid organ transplantation have several limitations in their study design. In particular, several systematic reviews exhibit notable constraints:

– the role of miRNAs is often examined within a single type of transplantation [6];
– investigations into the involvement of miRNAs in mechanisms of organ injury are frequently conducted in broader pathological contexts, with transplant recipients representing only a subset of the overall cohort [7];
– the role of miRNA in the development of specific complications is currently being studied [8].

These observations underscore the need for a comprehensive analysis of contemporary literature on the role of miRNAs in transplant medicine, particularly in the context of their involvement in complex immune response cascades and mechanisms of graft injury.

Objective: to systematize and critically analyze published data on miRNAs as key elements of epigenetics, as well as to evaluate their clinical significance in solid organ transplantation.

METHODOLOGY FOR LITERATURE SEARCH

The literature search was conducted using major electronic scientific citation databases – PubMed (www.ncbi.nlm.nih.gov/pubmed) and Russian Science Citation Index (RSCI, https://www.elibrary.ru).

To construct search queries in RSCI (last search date: September 20, 2025), the following keyword combinations (English and Russian words) were used: микроРНК* транспл* орган* эпигенетик*; microRNA* transplant* organ* epigenetic*; микроРНК* транспл* орган*; microRNA* transplant* organ*; микроРНК* транспл* печень*; microRNA* transplant* liver*; microRNA* transplant* renal*; микроРНК* транспл* почка*; microRNA* transplant* kidn*; микроРНК* транспл* сердце*; microRNA* transplant* heart*; микроРНК* транспл* легкие*; microRNA* transplant* lung*.

For the PubMed search (last search date: September 25, 2025), the following keyword combinations were used:: microRNA transplant organ; epigenetic transplant organ; microRNA transplant liver; microRNA transplant kidney; microRNA transplant renal; microRNA transplant heart; microRNA transplant lung.

The analysis included full-text reviews, meta-analyses, and original research articles published in Russian and English. Selected studies addressed the expression of various miRNAs in solid organ (heart, kidney, liver, and lung) transplantation, encompassing both clinical studies and experimental animal models. The literature review focused on the following key aspects:

– the relationship between miRNA expression and clinical outcomes of transplantation (development of pathological conditions/complications and patient survival);
– the diagnostic, prognostic, and therapeutic potential of miRNAs;
– methods for quantitative assessment of miRNA expression and interpretation of results across various loci;
– associations between miRNA levels and anthropometric and other recipient parameters;
– analysis of miRNA-mediated signaling pathways and their deleterious and protective effects on the graft;
– the relationship between miRNAs and the regimen and efficacy of immunosuppressive therapy;
– clinical applications.

The exclusion criteria for study selection were as follows:

– studies involving the use of miRNA in bone marrow or stem cell transplantation;
– studies focusing on DNA methylation;
– studies on histone modification;
– publications available only as preprints or conference proceedings;
– duplicate publications.

The overall structure of the literature search and study selection process is presented in Fig. 1.

All publications identified through the search queries across each database were evaluated for relevance to the objectives of the review and consolidated into a unified dataset. The subsequent stage involved the removal of duplicate publications and the exclusion of studies that did not meet the predefined inclusion criteria.

RESEARCH RESULTS

The initial search conducted in the eLIBRARY.RU database yielded 242 publications related to epigenetics and 1,199 publications addressing miRNA in the context of organ transplantation. A parallel search in PubMed identified 676 publications related to epigenetics and 1,541 publications focusing on miRNAs within the broader body of scientific literature.

The earliest publications addressing epigenetics in transplant medicine date back to 1988, with a marked increase in research activity and a peak in the number of publications observed between 2016 and 2020 (Fig. 2a). Studies using the term “microRNA” emerged later, beginning around 2009, with peak publication activity recorded in 2019 (Fig. 2b).

Following the application of inclusion and exclusion criteria, the final dataset comprised 305 publications, which were categorized into three principal groups:

– epigenetics and miRNAs in solid organ transplantation;
– miRNAs in the diagnosis and prognosis of complications;
– miRNA-based drugs, clinical applications.

Published studies clearly demonstrate the growing importance of investigating epigenetic mechanisms – particularly miRNA – in the development of pathological conditions in solid organ recipients.

However, despite increasing scientific interest, most available studies on the significance of these molecules in organ transplantation remain exploratory in nature. The translation of these findings into routine clinical practice is still limited by several important challenges:

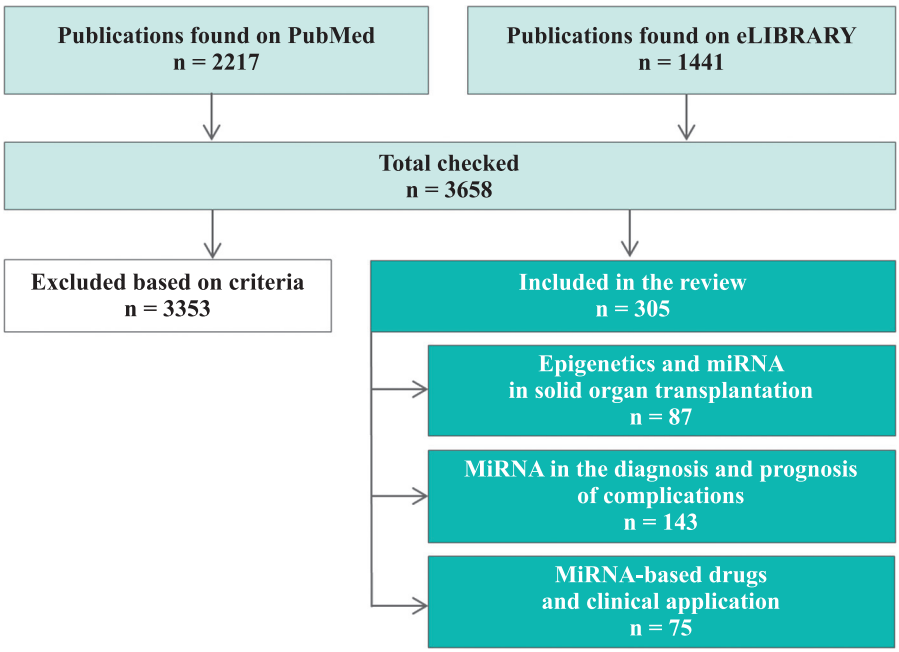
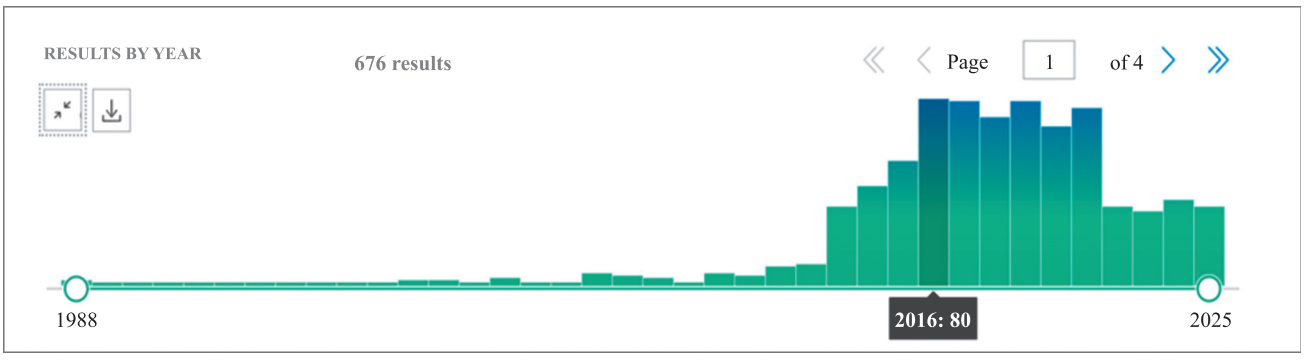


Fig. 1. Flow diagram of the literature selection process for the systematic review

a



b

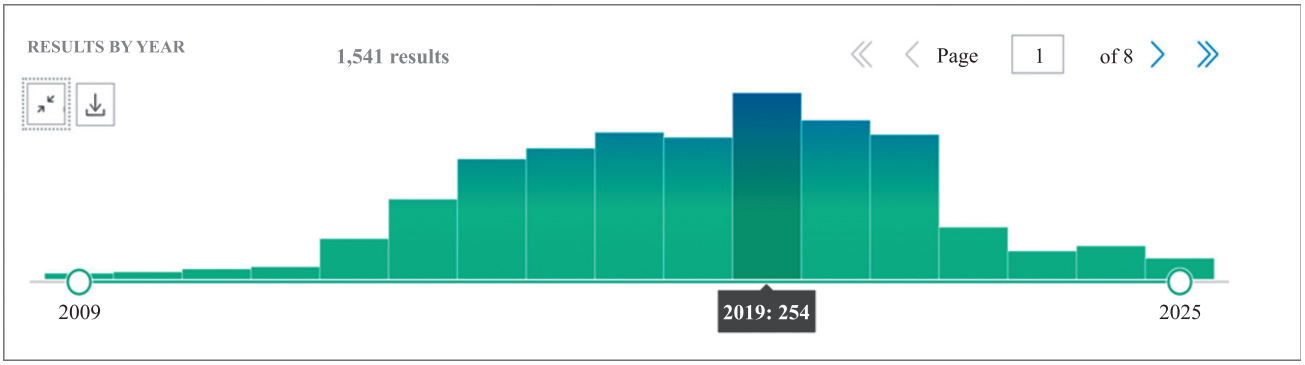


Fig. 2. Distribution by year of publications on PubMed for the following search queries: a) “epigenetic transplant organ”, b) “microRNA transplant organ”

the relatively small number of large-scale randomized and prospective clinical trials, lack of standardized and reproducible methods for quantitative assessment of miRNA expression, and inconsistencies in results reported across different studies. The latter is partly due to the large number of miRNA molecules and the pleiotropic nature of their effects in various tissues and organs.

EPIGENETICS AS A NEW FIELD OF SCIENCE

The term "epigenetics" was first introduced in 1942 by English biologist Conrad Waddington to describe the concept of the "epigenetic landscape", which illustrates the complex and dynamic interactions between environmental factors and the genome during the formation of phenotype [9]. Environmental influences can trigger intricate regulatory cascades that modulate gene activity. Some of these epigenetic modifications can be transmitted across several generations. In this way, the stability of the genetic code ensures species survival, while epigenetic mechanisms provide the flexibility required for adaptation to changing environmental conditions. These processes enable long-term programming of gene activity, including the selective activation or "silencing" of specific genes [10, 11].

Widespread scientific interest in epigenetics emerged at the turn of the 20th and 21st centuries, following experimental evidence demonstrating that organisms can, under environmental influence, inherit patterns of gene activity and subsequently "switch off" these patterns when the external stimulus is removed [12].

The discovery of the unique reversible nature of epigenetic modifications has fundamentally transformed classical views of genetics. Emphasizing the distinction between inherited genetic information and environmentally influenced gene regulation, the distinguished biologist and Nobel laureate Peter Medawar famously stated: "Genetics proposes; epigenetics disposes". This implies that, beyond the inherited genome, environmental exposures play a decisive role in shaping disease risk over an individual's lifetime and even across generations.

This concept has been experimentally illustrated in studies involving Drosophila melanogaster, where environmental factors such as temperature changes triggered the activation of specific chromosomal elements. As a result, the offspring's eye color changed from yellow to red.

In 2004, New Zealand researchers Peter Gluckman and Mark Hanson proposed the so-called "mismatch hypothesis", which suggests that during embryonic development, adaptive programming is initiated in response to environmental cues. This process allows the developing organism to "predict" future environmental conditions and adjust its physiology accordingly. If this prediction is confirmed, the resulting phenotype enhances survival; otherwise, unused adaptation may cause pathology [14].

Empirical support for this concept was provided by studies of individuals born during the Dutch famine of 1944–1945, conducted by epidemiologist Lammert van den Berg and colleagues. These investigations showed that women exposed to severe malnutrition during the third trimester of pregnancy later gave birth to children with reduced anthropometric measures. Despite being raised in relatively favorable postnatal conditions, these individuals exhibited a significantly increased risk of obesity, type 2 diabetes, and hypertension in adulthood compared with those born to well-nourished mothers [15].

This phenomenon was attributed to prenatal metabolic programming – often referred to as fetal "imprinting" – occurring during late gestation, in which intrauterine prediction of famine conditions and the activation of a gene responsible for enhanced nutrient storage in the fetus. Even more remarkable was the fact that the next generation inherited both the anthropometric characteristics of their undernourished parents and the incidence of disease in adulthood.

These fundamental discoveries have provided a new framework for understanding common diseases by distinguishing between purely genetic disorders and those driven by epigenetic alterations. This distinction has important implications for the potential reversibility of pathological processes, making it highly relevant from a national public healthcare perspective. To date, substantial evidence has linked epigenetic dysregulation to the development of oncological, metabolic, and autoimmune diseases.

THE FORMATION OF DOMESTIC EPIGENETICS

The development of epigenetics in Russia has been quite challenging. Nevertheless, our compatriots have made significant contributions to this rapidly evolving field. Among them, Boris Vanyushin (1933–2019) is widely regarded as a foundational figure in early Soviet epigenetic research. His work laid important groundwork for contemporary studies in gerontology, oncology, and biotechnology.

As early as the 1970s, Vanyushin and his team were among the first to demonstrate that methyl groups attached to cytosine residues in DNA play a critical role in gene silencing, and that these DNA methylation patterns are influenced by environmental factors such as stress and nutrition, as well as developmental processes. They also identified DNA hypomethylation as a key mechanism in tumorigenesis, characterized by disruption of normal methylation patterns in cancer cells and subsequent activation of oncogenes [16].It was this revolutionary discovery that anticipated modern research into the role of the epigenome in oncogenesis. The ideas about the connection between methylation and cancer, put forward at the end of the last century, became the basis for the development of DNA methyltransferase

inhibitors (e.g., azacitidine), used today in the treatment of leukemia. Later, in the 1980s, Vanyushin also described age-associated accumulation of methylation errors, linking epigenetic drift to cellular aging and proposing the concept of age-dependent methylation changes [17].

At the same time, significant advances in the study of epigenetics of stress in plants and animals have been achieved in our country, with the aim of improving agricultural productivity.

Experimental work conducted by Vladislav Khlobovich at the Institute of Cytology and Genetics (Siberian Branch of the Russian Academy of Sciences, Novosibirsk) demonstrated that extreme environmental stressors such as drought and cold can influence the heritable regulation of gene activity in agricultural crops [18].

As a result of a series of experiments, a wheat variety resistant to soil salinization was developed, but more importantly, the possibility of so-called epigenome reprogramming became evident [19].

At the beginning of the 21st century, both in Russia and globally, the advent of whole-genome sequencing technologies marked a major technological breakthrough. These methods, together with advances in molecular profiling and systems biology, significantly expanded the understanding of epigenetic mechanisms and helped define new directions in biomedical and biological research worldwide.

KEY EPIGENETIC MECHANISMS

Epigenetic mechanisms regulate organismal development and cell differentiation, ensuring genomic flexibility and adaptability. They enable cells to respond to changes in environmental conditions through biochemical reactions controlled by specific enzymes [20]. Dysregulation of epigenetic processes is closely associated with a wide range of pathologies.

Three main mechanisms of epigenetic modification are distinguished: genomic mechanisms involving DNA methylation mediated by enzymes; proteomic mechanisms involving post-translational modifications of histones in their unstructured N-terminal domains; and transcriptomic mechanisms involving regulation of gene expression via microRNA molecules.

These processes not only interact to shape the structural and functional organization of chromatin but also complement one another, thereby ensuring the reliability of epigenetic signal transmission.

DNA methylation is the process by which a methyl group (CH_3) is added to cytosine in the presence of guanine, typically within CpG dinucleotides, forming a covalent modification at these sites. The primary biological role of this process is the suppression of transposon transcription ("jumping genes", which constitute up to 45% of the human genome). Uncontrolled transposon activity may lead to genome instability, chromosomal abnormalities, immunodeficiency, and oncogenic transformation of cells [20]. As a central epigenetic mechanism, CpG site methylation contributes to genome stability by regulating transposon activity and maintaining long-term silencing of genes essential for normal development and physiological function.

Histone modification is a regulatory mechanism involving chemical alterations of histone proteins, which are responsible for DNA packaging within the nucleus, chromatin organization, and regulation of gene activity. Histones control the accessibility of DNA regions for transcription, while the degree of chromatin compaction and gene expression depends on various post-translational modifications, including methylation, phosphorylation, and ubiquitination [12, 21]. Combinations of these modifications form the so-called "histone codes", which regulate tissue-specific gene expression.

MicroRNA molecules. Another epigenetic mechanism of gene expression regulation is mediated by RNA interference and involves small non-coding miRNAs, typically 18–25 nucleotides in length. MiRNAs are relatively stable molecules that circulate freely in tissues and biological fluids. According to various estimates, the number of miRNA molecules in the human body may reach approximately 37,000, each of which can regulate multiple target genes simultaneously, forming complex networks of molecular interactions.

IMPORTANCE FOR TRANSPLANT MEDICINE

Epigenetic dysregulation is known to be directly or indirectly associated with the development of various pathological conditions. Within this paradigm, exploring the potential practical application of epigenetic criteria in the field of organ and tissue transplantation appears highly promising. In particular, the identification of novel epigenetic biomarkers of graft rejection and tissue remodeling may provide valuable opportunities for early diagnosis and prediction of post-transplant complications.

The theory of age-dependent methylation [22] has been confirmed by researchers worldwide and served as the basis for the development, in 2013, of an algorithm by American biologist Steve Horvath for assessing the biological age of tissues and organs based on analysis of 353 DNA regions, known as the "epigenetic clock" [23, 24].

It has been shown that the rate of aging of organs and tissues does not always correlate with the chronological age of the organism. Applied to transplantation medicine, this concept suggests that the epigenetically determined "biological age" of a donor organ may serve as a promising independent criterion for donor selection, a predictor of transplant outcomes, and a factor guiding postoperative management strategies in recipients.

The study of the relationship between miRNA and parthanatosis – a form of programmed cell, tissue, and organ death – has also shown significant promise. A correlation has been identified between pre-transplant

miRNA expression levels, cellular aging pathways, and clinical outcomes after transplantation. These findings support the concept of minimally invasive preoperative prediction of outcomes in recipients of heart, kidney, liver, and lung transplants [25].

Patients who have undergone organ transplantation require lifelong immunosuppressive therapy to prevent graft rejection; however, this treatment is associated with an increased long-term risk of malignant tumors and other adverse effects. A key mechanism underlying this risk is epigenetic "silencing" of tumor suppressor genes through promoter hypermethylation [26].

Current research is therefore focused on developing safe epigenetic drugs and biomarkers for early cancer detection, including malignancies associated with prolonged immunosuppressive therapy, which is of critical importance for transplant recipients.

A deeper understanding of the complex interactions between epigenetic alterations, immune responses, and post-transplant pathological processes opens new perspectives for personalized targeted therapy, aimed at long-term, individualized modulation of the recipient's epigenome [27, 28].

MICRORNA IN THE DIAGNOSIS AND PROGNOSIS OF TRANSPLANT PATHOLOGY

The study of potential biomarkers at the pre-translational level represents a qualitatively new step in the early diagnosis of post-transplant complications. In this context, transcriptome analysis enables the identification of miRNA expression profiles that can not only stratify patients according to their immunological risk of rejection or tolerance but also differentiate between types of rejection, thereby providing clinically relevant information for treatment decisions and indications for additional instrumental investigations, including biopsy [29, 30].

A growing number of studies highlight the significance of miRNAs in cardiovascular diseases and in acute rejection of transplanted organs [31, 32]. Because miRNAs regulate key signaling pathways, changes in individual miRNA levels in donor organ tissues or recipient biological fluids correlate with the presence and severity of graft injury. Alterations in miRNA profiles have been detected not only in plasma and serum but also in biopsy samples from transplant recipients with acute cellular rejection. The observation that certain miRNAs originate from immune cells rather than graft tissue suggests that rejection may be predicted even before overt organ damage occurs [33].

Although biomarker levels may be influenced by non-specific factors, consistent changes in circulating miRNA profiles during solid organ rejection, mediated through defined signaling pathways, support their potential utility as both diagnostic and therapeutic targets [34].

Table 1 summarizes the main findings of studies demonstrating the clinical relevance of miRNA expression in complications following heart, lung, kidney, and liver transplantation.

Every year, researchers identify new miRNAs with diagnostic and prognostic relevance for post-transplant complications. Notably, rejection mechanisms in different solid organs are associated either with distinct miRNA expression profiles or, conversely, with the involvement of specific miRNAs in multiple pathological processes across different patient groups, as demonstrated by numerous studies.

An analysis of recent literature shows that most research on miRNAs has focused on heart and kidney transplant recipients, followed by liver transplantation. The smallest number of studies concerns lung transplantation, likely due to both the lower overall number of lung transplants and the challenges associated with assessing graft function and validating research findings.

In heart transplantation specifically, several dozen miRNAs associated with acute rejection have been identified. Their expression levels are most often quantified using PCR-based methods in plasma or serum samples collected from recipients at different time points after transplantation. Variability in the biological material used is partly explained by differences in reagent systems produced by various manufacturers for quantitative miRNA assessment.

The most common of these include miR-10a, miR-31, miR-92a, and miR-155 [35, 44]. Sukma Dewi and other authors have also demonstrated that levels of miR-142-3p, miR-144-3p, miR-101, miR-326, and miR-101-3p may help identify heart transplant recipients with acute cellular rejection [6, 37, 41].

In several studies, Shevchenko et al. reported the diagnostic value of miR-101 and miR-27 in acute rejection of transplanted hearts. In particular, miR-101 levels may allow prediction of rejection even at the preoperative evaluation stage of potential recipients [39, 43]. Additionally, altered miR-27 expression has been associated with myocardial fibrosis, together with changes in miR-339 [40].

Singh et al. described an association between miR-126 and miR-200 expression in recipient blood plasma and the development of cardiac allograft vasculopathy, highlighting their potential role in predicting this complication.

Changes in miR-424 levels in plasma samples from heart and lung transplant recipients have also been observed during Gram-negative bacteremia caused by antibiotic-resistant pathogens, which represent a serious threat in immunocompromised patients receiving lifelong immunosuppressive therapy [42]. In this study, a significant increase in miR-424 levels was detected following confirmation of bloodstream infection.

Table 1

Key findings on the clinical significance of miRNAs in solid organ transplantation (heart, lungs, kidney, liver)

s/n	Authors, reference	Year	Significant miRNAs	MiRNA expression site	Clinical significance
Heart					
1	Duong Van Huyen J.P. et al. [35]	2014	miR-10a miR-31 miR-92a miR-155	Blood serum, transplant tissue	Diagnosis of rejection
2	Singh N. et al. [36]	2015	miR-126 miR-200	Blood plasma	Prognosis of allograft vasculopathy
3	Sukma Dewi I. et al. [37]	2017	miR-142-3p miR-101-3p	Blood serum	Diagnosis of rejection
4	Neumann A. et al. [38]	2017	miR-628-5p	Blood plasma	Diagnosis of vasculopathy
5	Velikiy et al. [39]	2020	miR-101 miR-27	Blood plasma	Diagnosis of acute rejection
6	Shevchenko et al. [40]	2021	miR-27 miR-339	Blood plasma	Diagnosis of myocardial fibrosis
7	Pérez-Carrillo L. et al. [41]	2022	miR-144-3p	Blood serum	Diagnosis and prognosis of acute cellular rejection
8	Shevchenko et al. [42]	2022	miR-424	Blood plasma	Diagnosis of Gram-negative bacteremia
9	Shevchenko et al. [43]	2023	miR-101	Blood plasma	Preoperative prognosis of rejection
10	Bansal S. et al. [44]	2024	miR-155	Blood plasma	Diagnosis of rejection
Lungs					
11	Gharib S.A. et al. [45]	2015	117 miRNA molecules	Epithelial cells	Diagnosis of acute cellular rejection
12	Zhu L. et al. [46]	2018	miR-199b-5p	Blood plasma	Anti-inflammatory effect in rejection
13	Dong M. et al. [47]	2019	miR-27a-3p	transplant tissue	Diagnosis of chronic rejection, obliterative bronchiolitis
14	Palleschi A. et al. [48]	2020	let-7f-5p miR-146b-3p miR-22-5p miR-29c-5p miR-362-5p miR-452-5p	Bronchoalveolar lavage fluid	Diagnosis of acute respiratory distress syndrome and graft dysfunction
15	Shevchenko O. et al. [49]	2021	miR-339	Blood plasma	Diagnosis of bronchial obstruction
16	Dong M. et al. [50]	2023	miR-27a-3p	Blood plasma	Diagnosis and prognosis of obliterative bronchiolitis syndrome
17	Yang J. et al. [51]	2025	miR-124-3p	Blood plasma	Diagnosis of acute graft injury
Kidney					
18	Danger R. et al. [52]	2013	miR-142-5p	Blood plasma	Diagnosis of chronic antibody-mediated rejection
19	Sui W. et al. [53]	2014	miR-181a miR-483-5p miR-557	Blood serum	Prognosis and diagnosis of rejection
20	Vahed S.Z. et al. [54]	2017	miR-150 miR-192 miR-200b miR-423-3p	Blood plasma	Diagnosis of chronic graft dysfunction
21	Cabral A. et al. [55]	2019	miR-27a-5p miR-331-3p miR-885-5p	Blood serum	Prognosis of transplant tolerance
22	de Necochea Campion R. et al. [56]	2025	let 7a-5p miR-29b-3pb miR-99a5p miR-148b-3p miR-148a-3p	Perfusate	Prognosis of graft dysfunction

Continuation Table 1

s/n	Authors, reference	Year	Significant miRNAs	MiRNA expression site	Clinical significance
Liver					
23	Wei L. et al. [57]	2013	miR-21 miR-155	Blood plasma	Diagnosis of rejection
24	Ruiz P. et al. [58]	2020	miR-122 miR-155 miR-181	Blood plasma	Diagnosis of acute cellular rejection
25	Koch P.F. et al. [6]	2024	miR-483-3p miR-885-5p	Blood plasma, Organ tissue	Diagnosis of acute cellular rejection
26	Julian J. et al. [59]	2025	miR-122-5p miR-181a-5p miR-101155-5p	Blood plasma	Diagnosis of rejection
27	Anam M. et al. [60]	2025	miR-452-5p miR-224-5p	Perfusate	Diagnosis and prognosis of rejection
Evaluation of various transplanted organs in a single study					
28	Zhou M. et al. [61]	2016	Liver: miR-22 miR-125b miR-99a miR-192	Organ tissue	Prognosis of graft dysfunction
			Heart: miR-1 miR-133a miR-296 miR-208 miR-499	Organ tissue	Diagnosis and prognosis of cardiovascular events
			Kidney: miR-126 miR-152 miR-182 miR-192 miR-194 miR-204 miR-215 miR-216	Urine	Diagnosis of graft dysfunction and cancer
			Lungs: let-7b miR-16 miR-26a miR-92 miR-125a miR-125b miR-200c	Organ tissue	Diagnosis of tissue fibrosis and cancer
29	Harris A., Krams S.M., Martinez O.M. [62]	2010	Kidney: miR-142-5p miR-155 miR-223	Organ tissue	Cancer prognosis
			Liver: miR-155	Organ tissue	Prognosis of rejection
30	Mas V.R. et al. [63]	2013	Liver: miR-30e miR-296	Perfusate	Diagnosis of graft dysfunction
			Kidney: miR-142-5p miR-155 miR-223	Urine	Prognosis of rejection

End of Table 1

s/n	Authors, reference	Year	Significant miRNAs	MiRNA expression site	Clinical significance
31	Amrouche L., Rabant M., Anglicheau D. [64]	2014	Heart: miR-133a miR-133b miR-208a	Blood plasma	Diagnosis of cardiovascular events
			Liver: miR-30b miR-34a miR-155 miR-222 miR-361 miR-455	Blood plasma	Diagnosis of fibrosis
			Kidney: miR-99a miR-200b miR-200 miR-142-3p	Urine	Prognosis of fibrosis
32	Hamdorf M., Kawakita S., Everly M. [65]	2017	Heart: miR-326 miR-142-3p miR-101	Blood serum	Diagnosis of rejection
			Liver: miR-122 miR-148a miR-194	Blood serum	Diagnosis of rejection
			Lungs: miR-126 miR-146a	Blood serum	Diagnosis of rejection

The diagnosis of lung rejection and fibrosis remains a fundamentally complex issue in transplant medicine, as transbronchial biopsy used to confirm pathological changes and associated graft dysfunction is an invasive procedure with a significant risk of bleeding, bacterial and fungal infections, and other complications. In this context, the development of minimally invasive approaches for monitoring rejection and structural graft changes is of critical importance.

Palleschi et al. demonstrated the involvement of let-7f-5p, miR-146b-3p, miR-22-5p, miR-29c-5p, miR-362-5p, and miR-452-5p in the diagnosis of acute respiratory distress syndrome and graft dysfunction. In this study, miRNA expression was analyzed in bronchoalveolar lavage samples [48].

Attempts to identify biomarkers of acute cellular rejection were also made by a group led by Gharib; however, the 117 miRNAs identified were assessed in epithelial cells, which does not fully meet the criteria for minimally invasive diagnostics [45]. Similarly, Dong et al. identified miR-27a-3p as a marker of chronic rejection and obliterative bronchiolitis, but this was initially performed in transplant tissue samples [47]. Subsequently, the same group evaluated miR-27a-3p levels in blood samples from lung transplant recipients, demonstrating its diagnostic and prognostic value for obliterative bronchiolitis syndrome [50].

Studies by Zhu and Yang demonstrated the involvement of miR-199b-5p and miR-124-3p in the development of acute lung injury and lung transplant rejection based on expression analyses in recipients' blood [46, 51].

The role of miR-339 in tissue fibrosis has also been studied in detail, providing the basis for further evidence of its involvement in bronchial obstruction after lung transplantation. The authors reported a significant increase in miR-339 levels in the plasma of lung recipients during the development of graft structural changes and bronchial stenosis, findings confirmed by invasive video-bronchoscopy [49]. They also noted that the diagnostic performance of miRNA testing improves when combined with measurement of the proteomic biomarker galectin-3.

Studies on the role of miRNAs in kidney transplantation have demonstrated a wide range of biological materials used for analysis, including graft tissue, plasma and serum, graft perfusate, and urine.

In a study by Sui, the analyzed miRNAs identified miR-181a, miR-483-5p, and miR-557 as effective blood markers for the diagnosis and prognosis of kidney transplant rejection [53]. According to Danger et al., chronic rejection can be identified through analysis of miR-142-5p in blood plasma [52].

Amrouche et al. showed a link between miR-142-3p, as well as miR-99a and the miR-200 family (miR-200b and miR-200), detected in urine, and kidney transplant fibrosis [64]. Studies by Mas and Harris further support the association of miR-142-5p with both graft rejection and cancer development [62, 63].

According to published data, miRNAs in liver transplantation are most frequently studied in recipients' blood plasma or in graft perfusate. Among the most relevant for detecting rejection are miR-122, miR-155, miR-181, miR-224-5p, miR-483-3p, miR-452-5p, and miR-885-5p [6, 57–60]. In addition, miR-30b, miR-34a, miR-155, miR-222, miR-361, and miR-455 have been identified as markers of fibrosis in the transplanted liver [64].

In Russian literature, there is significantly less data on the specific features of miRNA regulation in solid organ recipients compared with international studies, and most research on small non-coding RNAs focuses on their role in oncology.

Only a limited number of institutions in the Russian Federation are engaged in the study of miRNAs in transplant recipients. The leading center in this field is the Shumakov National Medical Research Center of Transplantology and Artificial Organs, Moscow, which has long been involved in the development of minimally invasive technologies for screening and detection of post-transplant complications [66–68].

The data presented reflect the diverse effects of various miRNAs, indicating the need for further studies in large patient cohorts to validate potential biomarkers and develop specific diagnostic panels for each specific type of pathology and transplant.

THE THERAPEUTIC POTENTIAL OF MICRORNA

The discovery of the link between miRNAs and a wide range of diseases has stimulated interest in their use as a novel class of therapeutic agents. This has driven significant interdisciplinary research across biology, chemistry, and medicine aimed at developing miRNA-based therapies. As a result, RNA-based therapy has emerged as a promising approach for treating cancer, while advances in RNA delivery systems have also contributed to the development of modern immunotherapeutic strategies, further accelerating innovation in the pharmaceutical industry.

The development of miRNA-based drugs is particularly promising due to their ability to selectively target specific molecular pathways and simultaneously regulate multiple genes within a single signaling pathway. This capacity enables the modulation of complex biological processes and opens broad prospects for clinical application. To date, miRNAs have been most extensively studied in oncology, with several candidate drugs currently undergoing various stages of clinical trials and regulatory evaluation [69].

To date, among the many miRNA molecules studied to varying extents, two main groups can be distinguished in terms of their medical applications: mimics and antagonists.

MiRNA mimics are synthetic molecules designed to replicate the function of endogenous miRNAs. They consist of short double-stranded RNA sequences which, once introduced into the cell, are incorporated into the RNA-induced silencing complex (RISC), similar to natural miRNAs. These mimics bind to target messenger RNAs and suppress their expression, thereby enabling regulation of specific protein levels. Their potential for correcting pathological conditions associated with miRNA dysregulation is currently under active investigation.

MiRNA antagonists are chemically modified oligonucleotides that inhibit target miRNAs. Commonly referred to as "anti-miRs" or "block-miRs", they function by binding to target miRNAs to disrupt translation.

In organ transplantation, miRNA-based therapies are being explored to improve recipient survival, reduce the risk of rejection, and mitigate ischemia–reperfusion injury in grafts. Table 2 presents examples of the use of miRNA mimics and antagonists across various fields of medicine, including solid organ transplantation, along with their observed therapeutic effects.

To date, several drugs based on RNA interference have been approved by the U.S. Food and Drug Administration and are in clinical use [82]. The international nonproprietary names of the active ingredients are:

– Patisiran – used for the treatment of hereditary transthyretin amyloidosis; one of the drug's RNA strands binds to messenger RNA transcribed from the TTR gene, thereby inhibiting transthyretin protein synthesis.
– Givosiran – used for the treatment of acute liver failure; a small interfering RNA suppresses the production of δ-aminolevulinic acid synthase (ALAS1) and participates in heme production, acting selectively on liver cells via the carbohydrate marker GalNAc and not entering cells of other organs [83].
– Lumasiran – used for the treatment of primary hyperoxaluria type 1; it targets the liver enzyme hydroxyacid oxidase 1, reducing oxalate levels in urine and plasma.
– Nedosiran – used for the treatment of primary hyperoxaluria type 1; it inhibits hepatic lactate dehydrogenase, an enzyme involved in oxalate production.
– Inclisiran – used for the treatment of primary hypercholesterolemia; it selectively targets the gene responsible for the production of proprotein convertase subtilisin/kexin type 9 (PCSK9) in the liver, enhancing hepatic uptake of circulating low-density lipoproteins and thereby reducing their blood levels [84].
– Vutrisiran – used for the treatment of hereditary and acquired transthyretin amyloid cardiomyopathy and

transthyretin amyloidosis with polyneuropathy; it inhibits messenger RNA regulating transthyretin production, leading to reduced serum TTR levels and decreased amyloid fibril deposition.

In addition, specialists at the Siberian State Medical University have developed a unique-in-its-class microRNA-based drug for the treatment of oncological diseases, aimed at inhibiting the transition of micrometastases into macrometastases [85]. This drug has successfully completed preclinical trials.

The data presented highlight the considerable potential of RNA-based therapies, particularly those leveraging RNA interference, for targeted treatment of various diseases. In the future, these approaches may be adapted to address the challenge of graft rejection in solid organ transplantation.

CHALLENGES AND PROSPECTS

The number of studies investigating the regulation of homeostasis and immune responses via miRNA continues to grow annually. However, a substantial gap remains in understanding the specific contribution of individual miRNAs to the pathogenesis of post-transplant complications. This is largely due to methodological and technological limitations inherent in miRNA research.

Only a limited number of candidate drugs have progressed to clinical trials, and some have been discontinued due to safety concerns, including toxicity. Further complexity arises from the fact that miRNAs participate in multiple interconnected signaling pathways, making it difficult to identify precise therapeutic targets and increasing the risk of unintended side effects.

In this context, continued research is essential to improve targeted delivery systems and optimize dosing strategies, with the goal of achieving maximal therapeutic efficacy while minimizing adverse effects.

Genomic technologies have enabled the identification of novel and effective biomarkers for transplant pathology. The growing volume of scientific publications has generated extensive datasets, while advances in information technology have created opportunities for their systematic analysis using machine learning algorithms. Improved analytical approaches now allow the integration and interpretation of large-scale medical data, facilitating the identification of complex and previously unrecognized patterns that are critical for understanding biological processes in transplant recipients [86, 87]. Using this genetic profiling approach, several clinically relevant biomarker panels have been developed. Among the most widely recognized are: AlloMap (used to identify patients at increased risk of heart transplant rejection by analyzing the expression levels of 11 genes in peripheral blood), AlloSure (a test based on donor-derived cell-free DNA (dd-cfDNA) for monitoring acute cellular

Table 2

MiRNA-based therapeutics: applications and observed therapeutic effects

Author, reference	Frug	Target	Therapeutic application	Effect
Mimetics				
Ryu Y. et al. [70]	MRX34	miR-34	Cancer therapy (hepatocellular carcinoma, melanoma)	Antitumor activity; clinical trials suspended due to high toxicity
Trang P. et al. [71]	let-7 mimetics	let-7	Lung cancer therapy	Suppression of tumor growth in preclinical studies
Zhao J.L. et al. [72]	miR-125a mimetics	miR-125a	Cancer therapy	Reprogramming of macrophages within the tumor microenvironment
Ramchandani D. et al. [73]	miR708-NP	miR-708	Cancer therapy	Suppression of tumor growth and metastasis
Chioccioli M. et al. [74] Montgomery R.L. et al. [75]	Remlarsen, MRG-229	miR-29	Liver and lung fibrosis therapy	Restoration of miR-29 levels and reduction of fibrosis in preclinical models
Antagonists				
Montgomery R.L. et al. [76]	anti-miR-208a	miR-208a	Heart failure therapy	Prevention of pathological cardiac remodeling and Myh7 activation in response to pressure overload
Thum T. et al. [77]	anti-miR-21	miR-21	Cardiovascular disease and cancer therapy	Inhibition of fibrosis and improvement of cardiac function in preclinical studies
Janssen H.L. et al. [78], Drury R.E. et al. [79], Bonneau E. et al. [80]	Miravirsen (RG-101)	miR-122	Hepatitis C therapy	Reduction of viral load in patients with hepatitis C
Seto A.G. et al. [81]	Cobomarsen (MRG-106)	miR-155	Cutaneous T-cell lymphoma (CTCL) therapy	Antitumor activity with good tolerability

rejection in heart and kidney transplant recipients; it can detect 266 single nucleotide polymorphisms through sequencing to accurately quantify the proportion of donor dd-cfDNA), and ImmuKnow Cylex (used to assess the level of immunosuppression in kidney transplant recipients [88].

Despite their clinical promise, these platforms have not yet been widely implemented in routine transplant practice. This limitation is largely due to their effectiveness primarily in detecting clinically manifest rejection, while remaining insufficiently sensitive for early identification of subclinical processes [89].

Moving beyond the concept that a single gene is linked to a single disease has led to the emergence of the modern framework of molecular networks and their integration within the body, encompassing, among other elements, the collective biological functions of microRNAs [90, 91]. It is likely that this approach will, over time, provide answers to some of the most complex questions in transplant medicine.

CONCLUSION

Epigenetics is a rapidly advancing field that has become firmly established in modern biotechnology, medicine, and agriculture. It investigates heritable properties of organisms that are not associated with changes in DNA sequence but are indirectly encoded within the genome. Epigenetic mechanisms – including DNA methylation, histone modifications, and regulation by miRNAs – play a central role in controlling gene expression, cell differentiation, and disease development. This field opens up new opportunities for both diagnosis and treatment.

Based on the results of this systematic review of the literature published in Russian and international electronic databases, focusing on the role of epigenetic mechanisms in solid organ transplantation, a clear and sustained trend toward the comprehensive development of this field of genetics is evident. Although the safety and efficacy of using miRNA as therapeutic targets remain to be fully established, the advantages of circulating miRNAs as diagnostic biomarkers are no longer in doubt.

Owing to their stable levels in the patient's body and their direct involvement in the epigenetic regulation of cellular function, miRNAs open new horizons for understanding the epigenetic determinism of potential organ recipients and donors regarding various transplant outcomes, thereby expanding the potential for effective targeted therapy for recipients.

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