

MicroRNAs as novel biomarkers for the diagnosis and treatment of pediatric diseases

Hwal Rim Jeong, MD, PhD¹, Il Tae Hwang, MD, PhD²

¹Department of Pediatrics, Soonchunhyang University College of Medicine, Cheonan, Korea; ²Department of Pediatrics, Hallym University Kangdong Sacred Heart Hospital, Hallym University College of Medicine, Seoul, Korea

MicroRNAs (miRNAs) are highly conserved noncoding RNAs that regulate gene expression by silencing or degrading messenger RNAs. Many of the approximately 2,500 miRNAs discovered in humans are known to regulate vital biological processes, including cell differentiation, proliferation, apoptosis, and embryonic tissue development. Aberrant miRNA expression may have pathological and malignant consequences. Therefore, miRNAs have emerged as novel diagnostic markers and potential therapeutic targets for various diseases. Children undergo various stages of growth, development, and maturation between birth and adulthood. It is important to study the role of miRNA expression in normal growth and disease development during these developmental stages. In this mini-review, we discuss the role of miRNAs as diagnostic and prognostic biomarkers in various pediatric diseases.

Key words: MicroRNA, Child, Biomarkers

Key message

MicroRNAs (miRNAs) are small noncoding RNAs that regulate gene expression post transcriptionally, and miRNA expression levels vary with developmental stages. miRNAs play an important role in several biological processes in children, including growth, neuro-development, inflammation, and tumor formation. Research on miRNAs may uncover the molecular mechanisms underlying various pediatric diseases, leading to the development of novel biomarkers that aid in the diagnosis, treatment, and prognosis of these diseases.

Introduction

MicroRNAs (miRNAs) are small, noncoding, single-stranded RNAs (18–23 nucleotides) that regulate posttranscriptional silencing of target genes through translational

repression or degradation of the target messenger RNA (mRNA).¹⁾ miRNAs were first discovered in 1993 in a study that demonstrated that *lin-4*, a regulator of larval developmental timing in the nematode *Caenorhabditis elegans*, does not code a protein, instead producing a pair of small RNAs.²⁾ It was subsequently found that the *lin-4* RNAs had antisense complementarity with multiple sites in the 3'UTR of *lin-14* gene, and could significantly reduce the quantity of LIN-14 protein.³⁾ These miRNAs have been shown to be conserved in several species, including humans. An increasing number of miRNAs have since been identified in animals, plants, and even viruses. These miRNAs regulate various biological processes, including developmental timing, cell death, cell proliferation, hematopoiesis, and nervous system patterning.⁴⁾

MiRNAs are abundant in several cell types, as well as in tissues and the circulation. Circulating miRNAs are released into body fluids, including blood, saliva, urine, breast milk, tears, and cerebrospinal fluid.^{5–7)} They can also be stably transported within extracellular vesicles, including apoptotic bodies, microvesicles, and exosomes. These vesicles are important for cell-to-cell communication because miRNAs can be selectively packaged, transported, and modulated for specific recipient cells.^{8,9)} miRNA expression levels may differ among different tissues and organs, and between physiological and pathological states. Dysregulated miRNA expression is related to several pathologies, including cardiovascular diseases, epilepsy, metabolic syndrome, cancer, allergies, and autoimmune diseases. Changes in miRNA levels can explain phenotypic differences and provide information about the underlying genetic pathways. Furthermore, miRNA analysis is advantageous because the molecules are highly resistant to degradation, and their expression levels can be assessed within a few hours using small biological samples. Since miRNAs are stable and easily measurable, they can be used as diagnostic and pro-

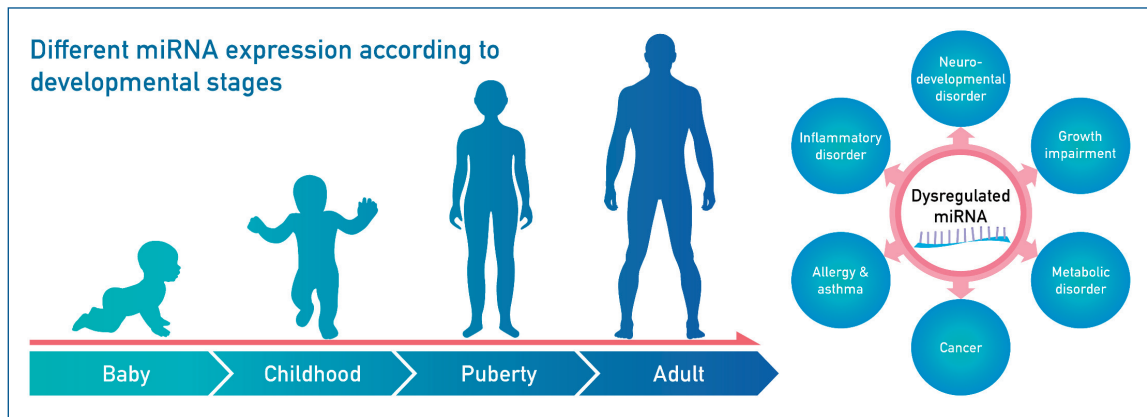
Corresponding author: Il Tae Hwang, MD, PhD. Department of Pediatrics, Hallym University Kangdong Sacred Heart Hospital, 150 Seongan-ro, Gangdong-gu, Seoul 05355, Korea

✉ Email: ithwang83@hallym.or.kr, <https://orcid.org/0000-0002-3885-4322>

Received: 26 January 2023, Revised: 22 April 2023, Accepted: 24 April 2023

This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Copyright © 2024 by The Korean Pediatric Society



Graphical abstract. MicroRNAs (miRNAs) are involved in the expression of genes that regulate normal human growth and development. Therefore, their dysregulation may lead to several diseases. miRNA research is important because miRNAs could serve as novel biomarkers for the diagnosis, progression, and prognosis of pediatric diseases.

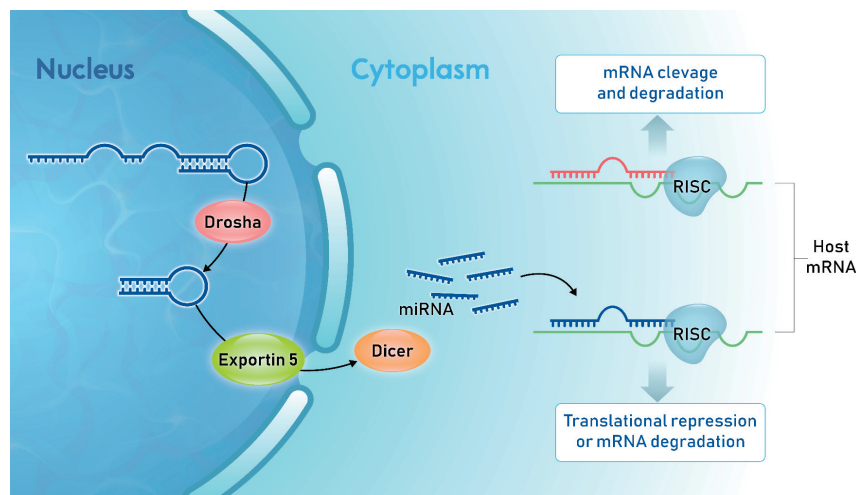


Fig. 1. MicroRNAs (miRNAs) biogenesis. mRNA, messenger RNA; RISC, RNA-inducing silencing complex.

gnostic biomarkers, as well as therapeutic targets.^{10,11)}

An increasing number of studies have investigated the role of miRNAs in pediatric diseases, but there is still a need for further research in this area. Although several studies have reported the efficacy of miRNAs as biomarkers, most of these studies were performed in adults, and the findings may not be applicable to children because of the role of ontogeny in disease evolution and the therapeutic response.¹²⁾ A noninvasive and convenient testing method is required for younger children. Therefore, the present study reviews miRNA research and discusses their potential role as biomarkers in pediatric diseases.

MiRNA biogenesis

In the nucleus, RNA polymerase II (Pol II) transcribes miRNA genes into long hairpin structures called primary miRNA (Fig. 1). DGCR8 and Drosha are RNA endonucleases that cleave the nucleotide from the primary miRNA

hairpin base to generate shorter precursor miRNA (pre-miRNA).

The nuclear pre-miRNAs are translocated by carrier protein Exportin-5 to the cytoplasm, where miRNA maturation occurs. Dicer ribonuclease with transactivation response element RNA-binding protein cuts away the loop of pre-miRNA to generate a mature miRNA duplex. This duplex consists of a guide strand (miRNA) and passenger strand (miRNA*) separated by a helicase. After miRNA* removal, mature miRNA is selected by the Argonaute 2 protein and incorporated into the RNA-induced silencing complex. Finally, the silencing complex binds to the mRNA molecule, usually at the 3'UTR of target mRNA, via sequence complementarity, resulting in cleavage degradation or translational repression of the mRNA.^{1,13,14)}

A single miRNA may potentially pair with hundreds of different mRNAs. Single miRNAs can pleiotropically target hundreds or thousands of genes and perform organ- or cell-specific functions.¹¹⁾ Similarly, each mRNA may be regulated by multiple miRNAs.¹⁵⁾ This multitargeting

property of miRNAs is advantageous for disease modification because of the possibility of disrupting several pathological processes simultaneously. However, this also increases the potential for unanticipated side-effects in miRNA-based therapies.¹⁶⁾ It is estimated that miRNAs regulate the expression of approximately 60% of human genes.¹⁷⁾

Age-related miRNA expression

MiRNA expression varies according to the developmental stage. Age-related miRNAs may be involved in biological pathways related to growth and development in children. Huen et al.¹⁸⁾ analyzed miRNA expression in Mexican-American children between birth and the age of 7 years. They found that, in contrast with the decrease in miRNA expression seen in the peripheral blood with age in adults,¹⁹⁾ the expression increased from birth to mid-childhood. Burgess et al.²⁰⁾ analyzed miRNA expressions in fetal, pediatric, and adult livers, and found that hepatic miRNA expression changes with age, particularly between the fetal and pediatric stages. They suggested that miRNA expression may contribute to the clinical variability seen in hepatic drug metabolism. Lai et al.²¹⁾ compared peripheral blood miRNA expression levels between preterm infancy and adulthood. About one-third of the miRNAs were constantly expressed from the postnatal period to adulthood, one-third were differentially expressed between preterm infants and adults, and the remaining one-third were not detectable in either sample. Although it may be difficult to generalize the results to other racial groups, they nevertheless improve our understanding of the relationship of peripheral blood miRNA expression changes with postnatal development and aging.

MiRNAs and growth

MiRNAs are involved in bone formation, including skeletal development, longitudinal bone growth, and chondrocyte proliferation and differentiation.²²⁾ MiRNAs are also critical for the regulation of hypothalamus function and pituitary development. They are known to be involved in growth hormone (GH) secretion and signaling pathways, including GH receptor (GHR) and insulin-like growth factor (IGF). Most of the evidence is based on animal models and in vitro studies, but there has been a recent increase in human studies, often overlapping with animal studies. Elzein and Goodyer²³⁾ reported that human GHR expression is regulated by miRNA-129–5p, miRNA-142–3p, miRNA-202, and miRNA-16, which reduce GHR mRNA and protein in human cancer cell lines and control cells. Among these miRNAs, miRNA-202,

and miRNA-16 are thought to regulate several aspects of the GH/IGF-1 axis. MiRNA-9 and miRNA-486 directly target IGF-1 3'UTR, leading to decreased IGF-1 expression at the mRNA and protein levels.^{24,25)} Gao et al.²⁶⁾ reported that most oral squamous cell carcinoma patients had significantly reduced let-7b expressions; let-7b suppresses cell growth by targeting IGF-1R and insulin receptor substrate-2.

An increasing number of studies on the association of the miRNA profile with growth impairment are being performed. A study of age-related serum miRNAs in untreated adult congenital GH-deficient patients demonstrated their involvement in insulin production, inflammation, and aging.²⁷⁾ An investigation of plasma miRNA expression in Chinese idiopathic short stature children demonstrated significant upregulation of miRNA-185 expression and downregulation of miRNA-497 expression.²⁸⁾ Mas-Parés et al.²⁹⁾ studied umbilical cord miRNA profiles associated with catch-up growth in small for gestational age (SGA) children. Umbilical cord miRNA-576-5p was associated with catch-up growth and cardio-metabolic risk in SGA children, indicating that it could serve as a novel biomarker for catch-up growth in SGA infants. A recent study by our group of the exosomal miRNA profile of SGA children also highlighted their potential role as prognostic biomarkers for catch-up growth in SGA children.³⁰⁾

Role of MiRNAs in diabetes and obesity

Several studies have reported miRNA dysregulation in patients with diabetes, obesity, and metabolic syndrome. The potential of miRNAs as biomarkers for diabetes and metabolic syndrome is being increasingly recognized.^{31–33)} Although studies comparing type 1 diabetes (T1D) patients with healthy controls have reported different miRNA expression signatures, but miRNA-21, miRNA-24, miRNA-148a, miRNA-181a–5p, miRNA-210–5p upregulation in T1D has been demonstrated in multiple independent studies.³⁴⁾ MiRNAs are associated with pancreatic β -cell damage, inflammatory cytokine production, and autoimmunity. MiRNA-204 is a highly enriched miRNA in human β -cells, and is released from dying β -cells into the serum. Serum miRNA-204 was increased in children with T1D, but not in those with type 2 diabetes, and was inversely correlated with cell functioning. Therefore, it could serve as a novel biomarker for T1D-associated β -cell damage.³⁵⁾

Obesity-induced chronic low-grade inflammation leads to insulin resistance, type 2 diabetes mellitus, and metabolic syndrome.^{36,37)} MiRNAs play a regulatory role in multiple processes, including insulin signaling, adipokine expression, adipogenesis, lipid metabolism, and diet regulation. A high-fat maternal diet during pregnancy and lactation in

mice resulted in altered hepatic miRNA-122 and miRNA-370 expression in the offspring.³⁸⁾ Dysregulated miRNA-122 and miRNA-370 expression has been shown to modulate hepatic lipid metabolism and contribute to metabolic disturbances. In a severely obese pediatric cohort, miRNAs 34a, 122, and 192 were correlated with obesity-associated inflammatory markers, including tumor necrosis factor- α , interleukin-1 receptor antagonist, procalcitonin, and adiponectin.³⁹⁾ In addition, the miRNA-122 concentration, which is correlated with homeostatic model assessment for insulin resistance and miRNA-192, was significantly elevated in obese participants. These miRNAs could serve as biomarkers for the unfavorable phenotype of childhood obesity, and may aid risk stratification for early intervention in childhood obesity.

Role of MiRNAs in cardiovascular disease

MiRNAs are also involved in cardiac development and function. Several miRNAs have been implicated in the development of the heart, and their dysregulation is associated with cardiovascular diseases, including congenital heart disease.^{40,41)} MiRNA-1 and miRNA-133 play a critical role in cardiac development, and miRNA-1 overexpression in the developing embryonic heart decreases the number of proliferating ventricular cardiomyocytes.⁴²⁾ In mice, miRNA-1-2 deletion was lethal in approximately 50% of the embryos because of ventricular septal defects, while around 20% of the survivors had major cardiac defects.⁴³⁾ MiRNA dysregulation has been reported in Down syndrome, the most common genetic cause of congenital heart defects. Overexpression in the heart of 5 human chromosome-21-derived miRNAs, including miRNA-99a, let-7c, miRNA-125b-2, miRNA-155, and miRNA-802, was also reported.⁴⁴⁾ MiRNA-99a was associated with the suppression of cardiogenesis, let-7c was found to induce cardiogenesis, and miRNA-155 overexpression was found to inhibit necrosis.

MiRNAs are also important in the pathogenesis, treatment, and prognosis of Kawasaki disease (KD), which is the primary cause of acquired heart disease among children in developed countries.⁴⁵⁾ MiRNA-223-3p overexpression has been reported in acute KD patients, in whom it may inhibit cytokines and alleviate vascular endothelial injury.⁴⁶⁾ Zhang et al.⁴⁷⁾ reported that lower miRNA-223 expression leads to severe coronary artery pathology in KD, and the presence of miRNA-223-3p may lead to the identification of patients at greatest risk for coronary artery pathology. As potential diagnostic biomarkers for KD, serum exosomal miRNA-1246, miRNA-4436b-5p, miRNA-197-3p, and miRNA-671-5p may be used to distinguish KD from other febrile conditions.⁴⁸⁾ Furthermore, serum exosomal miRNA-328,

miRNA-575, miRNA-134, and miRNA-671-5p could serve as biomarkers for KD and the outcomes of intravenous immunoglobulin therapy.⁴⁹⁾

MiRNAs are also potential biomarkers for the diagnosis of heart failure and acute myocarditis.⁵⁰⁻⁵²⁾ The diagnosis of myocarditis remains a challenge. Blanco-Domínguez et al.⁵¹⁾ reported that mmu-miRNA-721 is synthesized by Th17 cells, and is present in the plasma of mice with acute autoimmune or viral myocarditis, but not in those with acute myocardial infarction. They reported that a novel human noncoding RNA (hsa-Chr8:96) with a similar sequence is associated with myocarditis, even after adjustment for age, sex, ejection fraction, and serum troponin levels. The area under the receiver operating characteristic curve for hsa-Chr8:96 to differentiate acute myocarditis and myocardial infarction was 0.927 (95% confidence interval, 0.879–0.975), with a sensitivity and specificity of >90%. Therefore, miRNAs could serve as alternative noninvasive biomarkers for the diagnosis and prognosis of cardiovascular diseases in the pediatric population.

MiRNAs in asthma

Asthma, which is the most common chronic illness among children, has a complex etiology involving genetic susceptibility, host factors, and environmental exposure.⁵³⁾ Asthma is related to airway inflammation, tone control, and responsiveness, but the exact mechanism is unknown.⁵⁴⁾ Ibrahim et al.⁵⁵⁾ investigated Annexin A1 (ANXA1), an important anti-inflammatory mediator, and miRNA-196a-2, a targeted ANXA1 gene, in asthmatic children and controls. Asthmatic children had an increased serum ANXA1 level and decreased miRNA-196a-2 expression, indicating their role in asthma etiology and potential as diagnostic biomarkers and therapeutic targets. Tiwari et al.⁵⁶⁾ demonstrated differential miRNA expression in asthmatic children among the 4 seasons. In particular, miRNA-328-3p and let-7d-3p were significantly associated with seasonal asthma symptoms and allergies. In addition, miRNAs were associated with asthmatic airways, airway remodeling, and virus-induced exacerbations. Several studies have been conducted on miRNA dysregulation in asthma, and miRNAs have been proposed as biomarkers for asthma status, severity, and treatment response.

MiRNAs in hematologic cancers

MiRNA dysregulation is a hallmark of childhood cancer.⁵⁷⁾ The identification of molecular markers of pediatric tumors is important to predict prognosis, and may lead to the de-

velopment of novel therapeutic approaches. MiRNAs play an important role in hematopoiesis and leukemogenesis.

In 2022, Calin et al.⁵⁸⁾ reported frequent 13q14 deletions, and the downregulation of miRNA-15 and miRNA-16, in chronic lymphocytic leukemia. This was the first study of miRNA dysregulation associated with human disease. In 2004, the same group mapped 186 miRNAs and found that over 50% of the miRNA genes were located in cancer-associated genomic regions or fragile sites.⁵⁹⁾ In addition, they identified the specific miRNA profile for human B-cell chronic lymphocytic leukemia.⁶⁰⁾ In 2007, Mi et al.⁶¹⁾ analyzed the miRNA expression profiles of adult and pediatric cancer patients, and used them to accurately distinguish between acute lymphocytic leukemia and acute myeloid leukemia. In 2009, Ju et al.⁶²⁾ analyzed differential miRNAs expression between childhood B-cell precursor acute lymphocytic leukemia and normal marrow samples, and found that miRNA-222, miRNA-339, and miRNA-142-3p were overexpressed, while miRNA-451 and miRNA-373 were downregulated. The clinical importance of miRNA profiles has also been confirmed based on their association with specific acute lymphocytic leukemia subtypes, treatment resistance, and event-free survival. Some miRNAs can be used to monitor disease progression, predict drug sensitivity, and assess prognosis. The role of miRNAs has been extensively studied in acute myeloid leukemia, chronic myelogenous leukemia, and lymphomas. Therefore, miRNAs could serve as diagnostic and prognostic molecular markers, and treatment targets, in hematological cancers.

MiRNAs in epilepsy

Epilepsy is a common and severe neurologic disorder characterized by recurrent seizures, increased mortality rates, and decreased social participation and quality of life.¹⁶⁾ Although antiepileptic drugs may control seizures in many patients, about one-third of cases are drug-resistant. It is necessary to identify individuals at risk for epilepsy, and to develop biomarkers and targeted therapies. The first study on miRNAs in human epilepsy was conducted in 2010, and reported elevated hippocampal miRNA-146a levels in temporal lobe epilepsy patients.⁶³⁾ Since then, several studies have demonstrated that miRNAs are important regulators of gene expression in epilepsy.

Mooney et al.⁶⁴⁾ manually curated the "EpimiRBase" database to provide comprehensive and up-to-date information on studies related to miRNAs and epilepsy. This fully searchable database includes brain and blood miRNA profiling studies, as well as functional studies. Specific miRNAs in the cerebrospinal fluid and blood may act as useful biomarkers for different types of brain injury, in-

cluding prolonged seizures and refractory seizures.⁷⁾ Research on miRNAs may improve our understanding of the causes, treatments, and diagnosis of epilepsy.

Limitations of MiRNA studies

MiRNA research has several limitations. First, there are several methods for evaluating miRNAs, the most common of which are oligonucleotide microarray (microchip) and quantitative real-time reverse-transcription polymerase chain reaction (qRT-PCR). However, there is no gold standard for measuring miRNA expression.⁶⁵⁾ It is considered good practice to profile miRNAs by microarray followed by validation through qRT-PCR.⁶⁶⁾ However, there are no standard guidelines for performing and reporting such validation studies. Second, there is a lack of information about the effects of other factors, such as age, sex, sample type, ethnicity, and medications, on miRNA levels. Third, inconsistent standards for sample size calculation to ensure sufficient power, and a lack of reproducibility of results across studies, has led to skepticism regarding clinical applicability. Finally, the cost for miRNA research is still significant. Nevertheless, this is an exciting and growing area of research that is still in its early stages and remains relatively under-explored.

Conclusions

In this review, we have discussed the current evidence regarding the role of miRNAs in pediatric diseases. Although the field of miRNA research has advanced significantly over the past few years, it is still a promising area, especially in relation to pediatrics. Further research on miRNA expression may allow identification of novel biomarkers for the diagnosis, progression, and prognosis of pediatric diseases. The identification and characterization of disease-specific miRNAs and their targets may improve our understanding of the pathophysiology of these diseases at the molecular level and advance personalized pediatric medicine.

Footnotes

Conflicts of interest: No potential conflict of interest relevant to this article was reported.

Funding: This study was supported by the NRF grant, funded by the Korean government (MSIT; no. 2022R1G1A10 09727).

ORCID:

Hwal Rim Jeong  <https://orcid.org/0000-0001-7040-9600>

Il Tae Hwang  <https://orcid.org/0000-0002-3885-4322>

References

1. Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell* 2004;116:281-97.
2. Lee RC, Feinbaum RL, Ambros V. The *C. elegans* heterochronic gene *lin-4* encodes small RNAs with antisense complementarity to *lin-14*. *Cell* 1993;75:843-54.
3. Wightman B, Ha I, Ruvkun G. Posttranscriptional regulation of the heterochronic gene *lin-14* by *lin-4* mediates temporal pattern formation in *C. elegans*. *Cell* 1993;75:855-62.
4. Ambros V. The functions of animal microRNAs. *Nature* 2004;431:350-5.
5. Weber JA, Baxter DH, Zhang S, Huang DY, Huang KH, Lee MJ, et al. The microRNA spectrum in 12 body fluids. *Clin Chem* 2010;56:1733-41.
6. Kim SY, Yi DY. Components of human breast milk: from macronutrient to microbiome and microRNA. *Clin Exp Pediatr* 2020;63:301-9.
7. Kim SH, Chae SA. Promising candidate cerebrospinal fluid biomarkers of seizure disorder, infection, inflammation, tumor, and traumatic brain injury in pediatric patients. *Clin Exp Pediatr* 2022;65:56-64.
8. Kosaka N, Iguchi H, Yoshioka Y, Takeshita F, Matsuki Y, Ochiya T. Secretory mechanisms and intercellular transfer of microRNAs in living cells. *J Biol Chem* 2010;285:17442-52.
9. Zhang J, Li S, Li L, Li M, Guo C, Yao J, et al. Exosome and exosomal microRNA: trafficking, sorting, and function. *Genomics Proteomics Bioinformatics* 2015;13:17-24.
10. Galasso M, Sana ME, Volinia S. Non-coding RNAs: a key to future personalized molecular therapy? *Genome Med* 2010;2:12.
11. Bartel DP. MicroRNAs: target recognition and regulatory functions. *Cell* 2009;136:215-33.
12. Goldman J, Becker ML, Jones B, Clements M, Leeder JS. Development of biomarkers to optimize pediatric patient management: what makes children different? *Biomark Med* 2011;5:781-94.
13. Paul S, Ruiz-Manriquez LM, Ledesma-Pacheco SJ, Benavides-Aguilar JA, Torres-Copado A, Morales-Rodríguez JI, et al. Roles of microRNAs in chronic pediatric diseases and their use as potential biomarkers: a review. *Arch Biochem Biophys* 2021;699:108763.
14. Fan R, Xiao C, Wan X, Cha W, Miao Y, Zhou Y, et al. Small molecules with big roles in microRNA chemical biology and microRNA-targeted therapeutics. *RNA Biol* 2019;16:707-18.
15. Cai Y, Yu X, Hu S, Yu J. A brief review on the mechanisms of miRNA regulation. *Genomics Proteomics Bioinformatics* 2009;7:147-54.
16. Henshall DC, Hamer HM, Pasterkamp RJ, Goldstein DB, Kjems J, Prehn JHM, et al. MicroRNAs in epilepsy: pathophysiology and clinical utility. *Lancet Neurol* 2016;15:1368-76.
17. Cho WC. MicroRNAs as therapeutic targets and their potential applications in cancer therapy. *Expert Opin Ther Targets* 2012;16:747-59.
18. Huen K, Lizarraaga D, Kogut K, Eskenazi B, Holland N. Age-related differences in miRNA expression in Mexican-American newborns and children. *Int J Environ Res Public Health* 2019;16:524.
19. Ameling S, Kacprowski T, Chilukoti RK, Malsch C, Liebscher V, Suhre K, et al. Associations of circulating plasma microRNAs with age, body mass index and sex in a population-based study. *BMC Med Genomics* 2015;8:61.
20. Burgess KS, Philips S, Benson EA, Desta Z, Gaedigk A, Gaedigk R, et al. Age related changes in MicroRNA expression and pharmacogenes in human liver. *Clin Pharmacol Ther* 2015;98:205-15.
21. Lai CY, Wu YT, Yu SL, Yu YH, Lee SY, Liu CM, et al. Modulated expression of human peripheral blood microRNAs from infancy to adulthood and its role in aging. *Aging Cell* 2014;13:679-89.
22. Cirillo F, Catellani C, Lazzeroni P, Sartori C, Street ME. The role of microRNAs in influencing body growth and development. *Horm Res Paediatr* 2020;93:7-15.
23. Elzein S, Goodyer CG. Regulation of human growth hormone receptor expression by microRNAs. *Mol Endocrinol* 2014;28:1448-59.
24. Hu YK, Wang X, Li L, Du YH, Ye HT, Li CY. MicroRNA-98 induces an Alzheimer's disease-like disturbance by targeting insulin-like growth factor 1. *Neurosci Bull* 2013;29:745-51.
25. Peng Y, Dai Y, Hitchcock C, Yang X, Kassis ES, Liu L, et al. Insulin growth factor signaling is regulated by microRNA-486, an underexpressed microRNA in lung cancer. *Proc Natl Acad Sci U S A* 2013;110:15043-8.
26. Gao L, Wang X, Wang X, Zhang L, Qiang C, Chang S, et al. IGF-1R, a target of let-7b, mediates crosstalk between IRS-2/Akt and MAPK pathways to promote proliferation of oral squamous cell carcinoma. *Oncotarget* 2014;5:2562-74.
27. Saccon TD, Schneider A, Marinho CG, Nunes ADC, Nouredine S, Dhahbi J, et al. Circulating microRNA profile in humans and mice with congenital GH deficiency. *Aging Cell* 2021;20:e13420.
28. Zhao S, Zhong Y, Jiang YH, Yi ZW. Circulating microRNA expression in children with idiopathic short stature. *Zhongguo Dang Dai Er Ke Za Zhi* 2013;15:1104-8.
29. Mas-Parés B, Xargay-Torrent S, Bonmatí A, Lizarraaga-Mollinedo E, Martínez-Calcerrada JM, Carreras-Badosa G, et al. Umbilical cord miRNAs in small-for-gestational-age children and association with catch-up growth: a pilot study. *J Clin Endocrinol Metab* 2019;104:5285-98.
30. Jeong HR, Han JA, Kim H, Lee HJ, Shim YS, Kang MJ, et al. Exosomal miRNA profile in small-for-gestational age children: a potential biomarker for catch-up growth. *Genes (Basel)* 2022;13:938.
31. Kakleas K, Kossyva L, Korona A, Kafassi N, Karanasios S, Karavanaki K. Predictors of associated and multiple autoimmunity in children and adolescents with type 1 diabetes mellitus. *Ann Pediatr Endocrinol Metab* 2022;27:192-200.
32. Nieto T, Castillo B, Nieto J, Redondo MJ. Demographic and diagnostic markers in new onset pediatric type 1 and type 2 diabetes: differences and overlaps. *Ann Pediatr Endocrinol Metab* 2022;27:121-5.
33. Domouzoglou EM, Vlahos AP, Cholevas VK, Papafaklis MI, Chaliasos N, Siomou E, et al. Association of fibroblast growth factor 21 with metabolic syndrome and endothelial function in children: a prospective cross-sectional study on novel biomarkers. *Ann Pediatr Endocrinol Metab* 2021;26:242-51.
34. Kim M, Zhang X. The profiling and role of miRNAs in diabetes mellitus. *J Diabetes Clin Res* 2019;1:5-23.
35. Xu G, Thielen LA, Chen J, Grayson TB, Grimes T, Bridges SL Jr, et al. Serum miR-204 is an early biomarker of type 1 diabetes-associated pancreatic beta-cell loss. *Am J Physiol Endocrinol Metab* 2019;317:E723-30.

36. Kim JH, Lim JS. The association between C-reactive protein, metabolic syndrome, and prediabetes in Korean children and adolescents. *Ann Pediatr Endocrinol Metab* 2022;27:273-80.
37. Kim M, Kim J. Cardiometabolic risk factors and metabolic syndrome based on severity of obesity in Korean children and adolescents: data from the Korea National Health and Nutrition Examination Survey 2007–2018. *Ann Pediatr Endocrinol Metab* 2022;27:289-99.
38. Benatti RO, Melo AM, Borges FO, Ignacio-Souza LM, Simino LA, Milanski M, et al. Maternal high-fat diet consumption modulates hepatic lipid metabolism and microRNA-122 (miR-122) and microRNA-370 (miR-370) expression in offspring. *Br J Nutr* 2014;111:2112-22.
39. Lischka J, Schanzer A, Hojreh A, Ba-Ssalamah A, de Gier C, Valent I, et al. Circulating microRNAs 34a, 122, and 192 are linked to obesity-associated inflammation and metabolic disease in pediatric patients. *Int J Obes (Lond)* 2021;45:1763-72.
40. Tian J, An X, Niu L. Role of microRNAs in cardiac development and disease. *Exp Ther Med* 2017;13:3-8.
41. Islas JF, Moreno-Cuevas JE. A microRNA perspective on cardiovascular development and diseases: an update. *Int J Mol Sci* 2018;19:2075.
42. Zhao Y, Samal E, Srivastava D. Serum response factor regulates a muscle-specific microRNA that targets Hand2 during cardiogenesis. *Nature* 2005;436:214-20.
43. Zhao Y, Ransom JF, Li A, Vedantham V, von Drehle M, Muth AN, et al. Dysregulation of cardiogenesis, cardiac conduction, and cell cycle in mice lacking miRNA-1-2. *Cell* 2007;129:303-17.
44. Kuhn DE, Nuovo GJ, Martin MM, Malana GE, Pleister AP, Jiang J, et al. Human chromosome 21-derived miRNAs are overexpressed in down syndrome brains and hearts. *Biochem Biophys Res Commun* 2008;370:473-7.
45. Xiong Y, Xu J, Zhang D, Wu S, Li Z, Zhang J, et al. MicroRNAs in Kawasaki disease: An update on diagnosis, therapy and monitoring. *Front Immunol* 2022;13:1016575.
46. Wang X, Ding YY, Chen Y, Xu QQ, Qian GH, Qian WG, et al. MiR-223-3p alleviates vascular endothelial injury by targeting IL6ST in Kawasaki disease. *Front Pediatr* 2019;7:288.
47. Zhang Y, Wang Y, Zhang L, Xia L, Zheng M, Zeng Z, et al. Reduced platelet miR-223 induction in Kawasaki disease leads to severe coronary artery pathology through a miR-223/PDGFR β vascular smooth muscle cell axis. *Circ Res* 2020;127:855-73.
48. Jia HL, Liu CW, Zhang L, Xu WJ, Gao XJ, Bai J, et al. Sets of serum exosomal microRNAs as candidate diagnostic biomarkers for Kawasaki disease. *Sci Rep* 2017;7:44706.
49. Zhang X, Xin G, Sun D. Serum exosomal miR-328, miR-575, miR-134 and miR-671-5p as potential biomarkers for the diagnosis of Kawasaki disease and the prediction of therapeutic outcomes of intravenous immunoglobulin therapy. *Exp Ther Med* 2018;16:2420-32.
50. Yan H, Ma F, Zhang Y, Wang C, Qiu D, Zhou K, et al. miRNAs as biomarkers for diagnosis of heart failure: A systematic review and meta-analysis. *Medicine (Baltimore)* 2017;96:e6825.
51. Blanco-Domínguez R, Sánchez-Díaz R, de la Fuente H, Jiménez-Borreguero LJ, Matesanz-Marín A, Relano M, et al. A novel circulating microRNA for the detection of acute myocarditis. *N Engl J Med* 2021;384:2014-27.
52. Oh JH, Kim GB, Seok H. Implication of microRNA as a potential biomarker of myocarditis. *Clin Exp Pediatr* 2022;65:230-8.
53. Sharma R, Tiwari A, McGeachie MJ. Recent miRNA research in asthma. *Curr Allergy Asthma Rep* 2022;22:231-58.
54. Eder W, Ege MJ, von Mutius E. The asthma epidemic. *N Engl J Med* 2006;355:2226-35.
55. Ibrahim AA, Ramadan A, Wahby AA, Draz IH, El Baroudy NR, Abdel Hamid TA. Evaluation of miR-196a2 expression and Annexin A1 level in children with bronchial asthma. *Evaluation of miR-196a2 expression and Annexin A1 level in children. Allergol Immunopathol (Madr)* 2020;48:458-64.
56. Tiwari A, Wang AL, Li J, Lutz SM, Kho AT, Weiss ST, et al. Seasonal variation in miR-328-3p and let-7d-3p are associated with seasonal allergies and asthma symptoms in children. *Allergy Asthma Immunol Res* 2021;13:576-88.
57. Carvalho de Oliveira J, Molinari Roberto G, Baroni M, Bezerra Salomão K, Alejandra Pezuk J, Sol Brassesco M. MiRNA dysregulation in childhood hematological cancer. *Int J Mol Sci* 2018;19:2688.
58. Calin GA, Dumitru CD, Shimizu M, Bichi R, Zupo S, Noch E, et al. Frequent deletions and down-regulation of micro-RNA genes miR15 and miR16 at 13q14 in chronic lymphocytic leukemia. *Proc Natl Acad Sci U S A* 2002;99:15524-9.
59. Calin GA, Sevignani C, Dumitru CD, Hyslop T, Noch E, Yendamuri S, et al. Human microRNA genes are frequently located at fragile sites and genomic regions involved in cancers. *Proc Natl Acad Sci U S A* 2004;101:2999-3004.
60. Calin GA, Liu CG, Sevignani C, Ferracin M, Felli N, Dumitru CD, et al. MicroRNA profiling reveals distinct signatures in B cell chronic lymphocytic leukemias. *Proc Natl Acad Sci U S A* 2004;101:11755-60.
61. Mi S, Lu J, Sun M, Li Z, Zhang H, Neilly MB, et al. MicroRNA expression signatures accurately discriminate acute lymphoblastic leukemia from acute myeloid leukemia. *Proc Natl Acad Sci U S A* 2007;104:19971-6.
62. Ju X, Li D, Shi Q, Hou H, Sun N, Shen B. Differential microRNA expression in childhood B-cell precursor acute lymphoblastic leukemia. *Pediatr Hematol Oncol* 2009;26:1-10.
63. Aronica E, Fluiter K, Iyer A, Zurolo E, Vreijling J, Van Vliet E, et al. Expression pattern of miR-146a, an inflammation-associated microRNA, in experimental and human temporal lobe epilepsy. *Eur J Neurosci* 2010;31:1100-7.
64. Mooney C, Becker BA, Raoof R, Henshall DC. EpimiRBase: a comprehensive database of microRNA-epilepsy associations. *Bioinformatics* 2016;32:1436-8.
65. Koshiol J, Wang E, Zhao Y, Marincola F, Landi MT. Strengths and limitations of laboratory procedures for microRNA detection. *Cancer Epidemiol Biomarkers Prev* 2010;19:907-11.
66. Croce CM. Causes and consequences of microRNA dysregulation in cancer. *Nat Rev Genet* 2009;10:704-14.

How to cite this article: Jeong HR, Hwang IT. MicroRNAs as novel biomarkers for the diagnosis and treatment of pediatric diseases. *Clin Exp Pediatr* 2024;67:119-25.