MicroRNAs in chronic pediatric diseases (Review)

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Abstract. MicroRNAs are small non-coding RNAs with a length of 20-24 nucleotides. They bind to the 3'-untranslated region of target genes to induce the degradation of target mRNAs or inhibit their translation. Therefore, they are involved in the regulation of development, apoptosis, proliferation, differentiation and other biological processes (including hormone secretion, signaling and viral infections). Chronic diseases in children may be difficult to treat and are often associated with malnutrition resulting from a poor diet. Consequently, further complications, disease aggravation and increased treatment costs impose a burden on patients and their families. Existing evidence suggests that microRNAs are involved in various chronic non-neoplastic diseases in children. The present review discusses the roles of microRNAs in five major chronic diseases in children, namely, diabetes mellitus, congenital heart diseases, liver diseases, bronchial asthma and epilepsy, providing a theoretical basis for them to become therapeutic biomarkers in chronic pediatric diseases.

Contents

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Abbreviations: Pri-microRNA, primary microRNA; Pre-microRNA, precursor microRNA; CHD, congenital heart disease; BA, biliary atresia; ABCC2, adenosine triphosphate-binding cassette subfamily C member 2; CFLD, cystic fibrosis without liver disease; RhoA, Ras homolog family member A

Key words: microRNAs, chronic childhood diseases, childhood asthma, congenital heart disease, diabetes, epilepsy

1. Introduction

In the face of social-economic development, urbanization and the aging population, chronic diseases are becoming a global public health issue that is associated with premature death and disability (1). Chronic diseases are the leading cause of mortalities worldwide and have led to a 16% increase in childhood morbidity over the past few decades in the USA (1). Chronic diseases in children refer to non-communicable diseases that last for >3 months and are caused by factors associated with genetic metabolism, environment and an unhealthy diet. Children with chronic diseases undergo long-term medical treatment and inpatient care, have special dietary requirements and experience psychological and physical changes as well as learning difficulties owing to physical unfitness and absenteeism (2). In the majority of cases, conventional diagnostic methods can detect childhood diseases at an advanced stage (3). Given that microRNAs regulate most biological processes, they may serve as efficient diagnostic and therapeutic tools for chronic diseases in children (4).

MicroRNAs are small non-coding RNAs of 20-24 nucleotides in length that play an important role in regulating gene expression (5-7). Each microRNA can regulate several target genes simultaneously. Alternatively, the combination of multiple microRNAs can regulate the expression of multiple genes that of a single gene. A total of ~60% of human genes are regulated by microRNAs, which constitute 2-3% of the human genome (8). However, abnormal expression of microRNAs in different cells or tissues has been associated with the pathogenesis, progression and severity of multiple chronic diseases, including cardiovascular, neurodegenerative and endocrine diseases (9-13). Highly specific microRNAs found in body fluids, such as blood, saliva, urine and semen, may serve as important biomarkers and play an essential role in developing treatment strategies for various diseases (14). The present review mainly summarizes the role of microRNAs in chronic diseases in children, including diabetes mellitus, congenital heart disease (CHD), liver diseases, bronchial asthma and epilepsy (Table I) (15-43).

2. MicroRNA biogenesis pathway

MicroRNA biogenesis begins in the nucleus with the synthesis of a long hairpin structure called primary microRNA (Pri-microRNA) through RNA polymerase II-mediated transcription. Subsequently, a splicing complex consisting of Drosha and DGCR8 cleaves the Pri-microRNA to form a smaller stem-loop structure called precursor microRNA (Pre-microRNA). After the Pre-microRNA is translocated into the cytoplasm via Exportin 5, the RNA-binding protein and the RNase III endonuclease Dicer collectively produce a mature double-stranded RNA structure. Decapping enzymes separate the two RNA strands, resulting in the binding of the guide strand to Argonaute-guided RNA-induced silencing complex 2. Finally, the RNA-induced silencing complex-microRNA complexes recognize specific mRNAs through sequence complementarity, leading to the degradation of mRNAs or the inhibition of translation (44-49).

3. MicroRNAs in diabetes mellitus

Diabetes mellitus is characterized by hyperglycemia resulting from impaired secretion or function of insulin (50-52). Prolonged hyperglycemia may cause structural and functional damage to the eyes, kidneys, heart, blood vessels and nervous system (53,54).

Studies have suggested that microRNA-124a2 and microRNA-375 regulate the generation of pancreatic β-cells and are required for the normal formation of vertebrate islets (55,56). MicroRNA-375 is essential for the establishment and maintenance of healthy pancreatic endocrine cells in mice postnatally (57), and its deficiency may result in pancreatic cell defects and chronic hyperglycemia. In addition, microRNAs have been reported to regulate various physiological processes associated with diabetes mellitus, such as insulin synthesis, secretion and sensitivity and energy homeostasis (8,58). MicroRNA-15a reduces the levels of endogenous uncoupling protein-2 to increase oxygen consumption and decrease ATP production, thereby resulting in the positive regulation of β-cell function and insulin biosynthesis (59). Additionally, the microRNA-25/NEUROD1 axis prevents insulin biosynthesis by regulating the transcription of cell-specific genes (60). MicroRNA-375 is specifically expressed in pancreatic islets and regulates the secretion of insulin from isolated pancreatic cells (8). Its overexpression inhibits the translation of the cytoplasmic protein myotrophin to reduce insulin secretion by inhibiting the exocytosis of insulin granules (61). Mice lacking microRNA-375 have increased blood glucose levels and decreased pancreatic β-cell volume owing to impaired proliferation (57).

4. MicroRNAs in CHD

CHD is the most common type of birth defect in children, affecting 5.4-16.1 per 1,000 live births worldwide (62). It refers to an anatomical developmental disorder or abnormality of the heart and large blood vessels that occurs during the embryonic stage (63). Based on the clinical presentation, CHD is classified as cyanotic heart disease, septal defects and left-sided obstructive defects (64,65). At present, diagnostic methods, such as ultrasound-guided measurement of nuchal translucency, and biomarkers, such as β-human chorionic gonadotropin and pregnancy-associated plasma protein-A, are used to screen for fetal CHD. However, false-positive results are common owing to the non-specificity of these methods (66).

Although numerous microRNAs play an important role in regulating cardiac function (64,67-74), microRNA-1 is most commonly associated with CHD (75). In addition to regulating embryonic heart development, microRNA-1 targets the cardiac transcription factor heart- and neural crest derivatives-expressed protein 2, which is involved in cardiovascular development during the embryonic stage (76). In a previous study, mice with microRNA-1 deficiency were revealed to have excessive proliferation of cardiomyocytes and defects in cardiac conduction, indicating that dysregulation of microRNA-1 may contribute to CHD (77). Additionally, microRNAs serve as potential biomarkers in clinical settings owing to their stability in blood, urine and other biological fluids and their ability to resist degradation by RNA-degrading enzymes (78). Yu *et al* (79) indicated that microRNAs in maternal serum can be used to detect fetal CHD. Zhu *et al* (80) used reverse transcription-quantitative PCR followed by sequencing by oligonucleotide ligation and detection to demonstrate that microRNA-19b, microRNA-22, microRNA-29c and microRNA-375 are upregulated in fetal CHD.

5. MicroRNAs in liver diseases

Liver diseases in children are more complex and varied compared with those in adults because it is common for liver diseases to be underrecognized or diagnosed late in children; under-diagnosis of liver disease in children is largely due to the absence of symptoms in most cases, especially in the early stages (81). As the majority of liver diseases cannot be easily detected because they do not present obvious symptoms until the late stage of the disease, most patients develop severe liver fibrosis or cirrhosis before diagnosis, which seriously affects their health (82). Biopsy is considered the gold-standard method for diagnosing liver disease and fibrosis; however, it can lead to severe bleeding and pain owing to its invasiveness (83). In addition, biopsy is limited to a small area of the liver and results in sampling errors, thereby leading to a potentially inaccurate diagnosis of heterogeneously distributed liver diseases (84). Therefore, a non-invasive diagnostic method is required for accurate and safe assessment of the extent of liver disease and fibrosis. MicroRNAs are involved in regulating several biological and pathological processes in hepatocytes, and their aberrant expression is associated with different liver pathologies. For example, the serum levels of miR-138 and miR-143 are characteristic of liver fibrosis in its later stages (85). In addition, the expression profile of microRNAs is specific to different etiologies of liver disease in both adults and children (86). Therefore, microRNAs may be used as potential biomarkers for the diagnosis of liver diseases in children.

Biliary atresia (BA) refers to the complete fibrous obstruction of a part of or entire extrahepatic bile ducts, and it is the most common cause of cholestasis in newborns (87,88). Owing to a poor prognosis, its diagnosis

Table I. MicroRNAs in chronic pediatric diseases.

A, Diabetes mellitus

MicroRNAs	Mechanism	(Refs.)
MicroRNA-21	Increases apoptosis in β-cells	(15)
MicroRNA-25	Associated with residual β-cell function and glycemic condition	(16)
MicroRNA-375	Can be used as a biomarker of β-cell death and diabetes	(17)
MicroRNA-21/126/210	Indicates an early onset of diabetes-associated diseases	(18)

B, Congenital heart disease

MicroRNAs	Mechanism	(Refs.)
MicroRNA-142-5p/1275/4666a-3p/3664-3p	Can be used as a non-invasive biomarker	(19)
MicroRNA-29/17-92/106b-25/503/424	Disrupts target genes in cardiac development	(20)
MicroRNA-21/23a/23b/24	Can be used as a biomarker of cardiac damage in pediatric patients	(21)

C, Liver diseases

MicroRNAs	Mechanism	(Refs.)
MicroRNA-200b	Associated with the progression of liver fibrosis	(22)
MicroRNA-21	Promotes fibrosis through the PTEN/AKT axis in biliary atresia	(23)
MicroRNA-29	Upregulated in experimental biliary atresia	(24)
MicroRNA-222	Modulates liver fibrosis in biliary atresia	(25)
MicroRNA-124/200	Promotes cholangiocyte proliferation in cholestasis	(26)
MicroRNA-1187	Regulates hepatocyte apoptosis in acute liver failure	(27)
MicroRNA-15b/16	Mediates hepatocyte apoptosis in acute liver failure	(28)
MicroRNA-150/663/503	Associated with human liver regeneration	(29)
MicroRNA-21	Regulates TGF-β signaling and fibrogenesis in non-alcoholic steatohepatitis	(30)
MicroRNA-122	Influences hepatitis C viral replication	(31)

D, Bronchial asthma

MicroRNAs	Mechanism	(Refs.)
MicroRNA-let7	Associated with asthma severity degree	(32)
MicroRNA-155	Causes allergic asthma by increasing the proliferative response of T helper cells	(33)
MicroRNA-221	Enhances interleukin-4 secretion in mast cells	(34)
MicroRNA-146a/b/28-5p	Associated with severe asthma in patients	(35)
MicroRNA-323-3p	Affects T-cell responses in asthma	(36)
MicroRNA-221/485-3p	Regulates the pathogenesis of asthma	(37)
MicroRNA-1	Aids in the diagnosis of asthma exacerbation	(38)
MicroRNA-218-5p	Serves a protective role in eosinophilic airway inflammation	(39)

E, Epilepsy

MicroRNAs	Mechanism	(Refs.)
MicroRNA-181a	Exerts a neuroprotective response	(40)
MicroRNA-124/134	Serves as a potential target for anticonvulsant drugs in epileptic developing brains	(41)
MicroRNA-21	Regulates status epilepticus	(42)
MicroRNA-15a-5p	Inhibits hippocampal neuronal apoptosis	(43)
MicroRNA-135a-5p	Reduces cell survival in temporal lobe epilepsy	(19)

and treatment are challenging, with 70% of children with BA requiring a liver transplant for long-term survival (89). Mice with biliary obstruction exhibit upregulated expression of microRNA-let7a-5p (a 4-fold increase in expression compared with control mice), which is associated with the expression of adenosine triphosphate-binding cassette subfamily C member 2 (ABCC2). ABCC2 is needed for the biliary excretion of numerous endogenous and heterogeneous compounds and promotes bile flow independently of bile acids (90). Upregulation of microRNA-155 enhances pro-inflammatory activity via activating JAK2/STAT3 and suppressing cytokine signaling 1, whereas its downregulation reduces the incidence of BA (91). A study on mouse models of rhesus rotavirus infection-induced BA demonstrated that microRNA-222 regulates fibrosis by targeting protein phosphatase 2 regulatory subunit B-α (PPP2R2A); notably, microRNA-222 inhibits PPP2R2A dephosphorylation and promotes Akt activation (25). In addition, clinical trials have demonstrated that aberrant expression levels of microRNA-214, microRNA-19b, microRNA-222 and microRNA-21 are strongly associated with liver fibrosis in patients with BA (92-94). Single-nucleotide polymorphisms in microRNAs have been reported to affect the development and prognosis of various diseases. In particular, polymorphisms in microRNA-100 (rs1834306 A>G), microRNA-499 (rs3746444 A>G), microRNA-492 (rs2289030 G>C) and microRNA-938 (rs2505901 T>C) may contribute to BA susceptibility (95-97).

A clinical trial has demonstrated that circulating levels of microRNAs are higher in patients with cystic fibrosis without liver disease (CFLD; n=30) compared with in those with liver disease (n=52). In addition, reverse transcription-quantitative PCR has been used to test healthy children and children with CFLD (n=20). The results revealed that the combination of serum microRNA-122, microRNA-21 and microRNA-25 is clinically relevant for the early diagnosis of CFLD, whereas the combination of serum microRNA-210, microRNA-148a and microRNA-19a facilitates the early diagnosis of liver fibrosis non-invasively (98).

6. MicroRNAs in bronchial asthma

Asthma is a group of chronic inflammatory diseases (99,100) characterized by episodes of obstructed airflow and high airway sensitivity. It impacts the quality of life of patients by affecting lung development, and it may also represent a life-threatening condition (101). Although a number of factors may exacerbate the risk of asthma (such as exposure to air pollutants and dust-mite allergen), identifying a single direct cause is difficult (69). However, recent studies have suggested that multiple microRNAs influence the pathogenesis of asthma (102-104). A total of >339 million individuals have asthma worldwide, with the features being higher in children compared with in adults (105). Asthma in children is typically caused by environmental allergens or viral infections that lead to immunoglobulin E-dependent Th2-type allergic reactions involving eosinophils, mast cells, T lymphocytes, neutrophils, airway epithelial cells and their cellular components. These reactions eventually increase airway reactivity and reduce airflow (106).

MicroRNAs play an important role in the pathogenesis of asthma by regulating inflammation. For example, childhood asthma has been associated with the downregulation of let-7 microRNA family members and upregulation of microRNA-155, microRNA-21, microRNA-146a/b, microRNA-142-3p, microRNA-223 and microRNA-142-5p (107,108). Let-7 is a highly conserved microRNA family that is most abundantly expressed in the lungs. Reduced levels of let-7 microRNA family members have been reported in the ovalbumin-sensitized mouse model (109). Let-7 microRNA family members play a pro-inflammatory role in asthma by inhibiting the secretion of interleukin-13 (110).

MicroRNAs have been demonstrated to regulate airway remodeling in mouse models. Ras homolog family member A (RhoA) participates in airway remodeling by regulating the differentiation of mesenchymal stem cells. MicroRNA-133a decreases the expression of RhoA, leading to the shrinkage of bronchial smooth muscle cells (111).

In addition, microRNAs are potential therapeutic targets for asthma (101). Studies have demonstrated that microRNA inhibitors or synthetic microRNA oligonucleotides can be used to inhibit upregulated microRNAs (for example, microRNA inhibitors or synthetic microRNA oligonucleotides can be used to suppress microRNA-21, -106a, -126, -145, -155 and -221 to control aberrant cytokine expression and inflammation), and that increasing tissue-specific microRNA expression using microRNA inducers may be an alternative therapeutic strategy for asthma (112,113).

7. MicroRNAs in epilepsy

Epilepsy is a chronic condition characterized by abnormal neural discharge that leads to transient malfunctions in the brain (114). It is associated with sudden, spontaneously terminating, recurrent motor-sensory, mental and consciousness disorders (115). Epilepsy is the most common neurological disorder in children characterized by a persistent predisposition to developing seizures (116). Medical advancements (such as genetic testing, electroencephalography and neuroimaging) have improved the diagnosis, treatment and quality of life of children with epilepsy (114). However, delayed diagnosis and treatment may affect their health adversely.

A study on hippocampal sections revealed that temporal lobe epilepsy is associated with the increased expression of microRNA-135a-5p. Similarly, the expression of microRNA-135a-5p is upregulated in epileptiform discharges of neonatal rat hippocampal neurons. In addition, inhibition of caspase activity and apoptosis inhibitor 1 expression demonstrates that microRNA-135a-5p promotes apoptosis in the epileptic temporal lobe, thereby reducing cell survival (116).

In another study including 63 patients with temporal lobe epilepsy (mean age, 9.81±2.79 years), serum analysis revealed significantly reduced expression of microRNA-15a-5p. In addition, a primary hippocampal cell culture (without magnesium) from newborn rats was used to mimic temporal lobe epilepsy in children, and the results showed that overexpression of microRNA-15a-5p could attenuate temporal

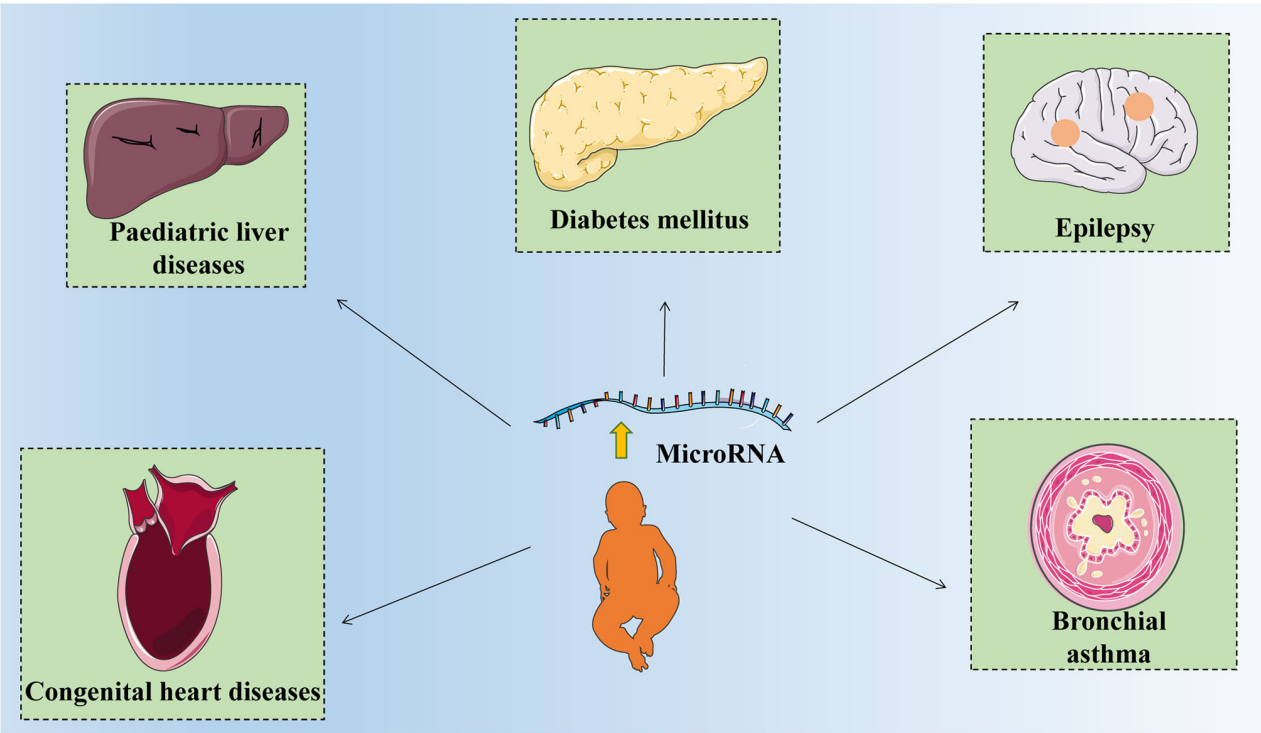

Figure 1. MicroRNAs serve roles in diabetes mellitus, congenital heart diseases, liver diseases, bronchial asthma and epilepsy in children, and therefore may be used as promising biomarkers for the diagnosis and treatment of chronic pediatric diseases.

lobe epilepsy-induced reductions in cell viability, and could reversed the cell apoptosis induced by temporal lobe epilepsy. This finding indicates that microRNA-15a-5p may serve as a highly specific and sensitive biomarker for the diagnosis of temporal lobe epilepsy in children (43).

Previous studies have reported that microRNAs are involved in the pathophysiology of epilepsy and represent an advanced tool for developing diagnostic and therapeutic strategies that are more effective and less invasive compared with traditional clinical strategies (drug treatment and ketogenic diet) (117-119). However, to the best of our knowledge, studies using microRNAs as diagnostic biomarkers for epilepsy, especially in children, are limited. An in-depth understanding of the role of microRNAs in early-stage epilepsy may guide the development of more rapid and accurate diagnostic strategies, as well as more effective prevention and therapeutic strategies for improving the quality of life of children with epilepsy.

8. Conclusion

The primary goal of pediatricians is to ensure the healthy and safe growth of children; however, children often develop chronic diseases, which are difficult to prevent and treat (120). MicroRNAs play a notable role in chronic diseases in children (121-124). To develop and classify microRNAs as effective biomarkers, further research is warranted to gain an in-depth understanding of the mechanisms and functional significance of various microRNAs in chronic diseases in children. Identification of disease-specific microRNAs and their target genes may guide the development of novel therapeutic strategies. Altogether, microRNAs serve as promising biomarkers for the diagnosis and treatment of chronic diseases in children (Fig. 1).

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Competing interests

The authors declare that they have no competing interests.

References

1. Perrin JM, Bloom SR and Gortmaker SL: The increase of childhood chronic conditions in the United States. JAMA 297: 2755-2759, 2007.
2. Janse AJ, Uiterwaal CSPM, Gemke RJBJ, Kimpen JLL and Sinnema G: A difference in perception of quality of life in chronically ill children was found between parents and pediatricians. J Clin Epidemiol 58: 495-502, 2005.
3. Omran A, Elimam D and Yin F: MicroRNAs: New insights into chronic childhood diseases. Biomed Res Int 2013: 291826, 2013.
4. Dong H, Lei J, Ding L, Wen Y, Ju H and Zhang X: MicroRNA: Function, detection, and bioanalysis. Chem Rev 113: 6207-6233, 2013.
5. Mohr AM and Mott JL: Overview of MicroRNA biology. Semin Liver Dis 35: 3-11, 2015.
6. Wu Y, Li Q, Zhang R, Dai X, Chen W and Xing D: Circulating microRNAs: Biomarkers of disease. Clin Chim Acta 516: 46-54, 2021.
7. Yoon JH, Abdelmohsen K and Gorospe M: Functional interactions among microRNAs and long noncoding RNAs. Semin Cell Dev Biol 34: 9-14, 2014.
8. Calderari S, Diawara MR, Garaud A and Gauguier D: Biological roles of microRNAs in the control of insulin secretion and action. Physiol Genomics 49: 1-10, 2017.
9. Romakina VV, Zhirov IV, Nasonova SN, Zaseeva AV, Kochetov AG, Liang OV and Tereshchenko SN: MicroRNAs as biomarkers of cardiovascular diseases. Kardiologiya 58: 66-71, 2018 (In Russian).
10. Ward BP, Tsongalis GJ and Kaur P: MicroRNAs in chronic lymphocytic leukemia. Exp Mol Pathol 90: 173-178, 2011.
11. Cao RY, Li Q, Miao Y, Zhang Y, Yuan W, Fan L, Liu G, Mi Q and Yang J: The emerging role of MicroRNA-155 in cardiovascular diseases. Biomed Res Int 2016: 9869208, 2016.
12. Lukiw WJ: microRNA-146a signaling in Alzheimer's disease (AD) and prion disease (PrD). Front Neurol 11: 462, 2020.
13. Fernandez-Valverde SL, Taft RJ and Mattick JS: MicroRNAs in β-cell biology, insulin resistance, diabetes and its complications. Diabetes 60: 1825-1831, 2011.
14. Wang K: The ubiquitous existence of MicroRNA in body fluids. Clin Chem 63: 784-785, 2017.
15. Sims EK, Lakhter AJ, Anderson-Baucum E, Kono T, Tong X and Evans-Molina C: MicroRNA 21 targets BCL2 mRNA to increase apoptosis in rat and human beta cells. Diabetologia 60: 1057-1065, 2017.
16. Nielsen LB, Wang C, Sørensen K, Bang-Berthelsen CH, Hansen L, Andersen ML, Hougaard P, Juul A, Zhang CY, Pociot F and Mortensen HB: Circulating levels of microRNA from children with newly diagnosed type 1 diabetes and healthy controls: Evidence that miR-25 associates to residual beta-cell function and glycaemic control during disease progression. Exp Diabetes Res 2012: 896362-896362, 2012.
17. Erener S, Mojibian M, Fox JK, Denroche HC and Kieffer TJ: Circulating miR-375 as a biomarker of β-cell death and diabetes in mice. Endocrinology 154: 603-608, 2013.
18. Osipova J, Fischer DC, Dangwal S, Volkmann I, Widera C, Schwarz K, Lorenzen JM, Schreiver C, Jacoby U, Heimhalt M, *et al*: Diabetes-associated microRNAs in pediatric patients with type 1 diabetes mellitus: a cross-sectional cohort study. J Clin Endocrinol Metab 99: E1661-E1665, 2014.
19. Wu X, Wang Y, Sun Z, Ren S, Yang W, Deng Y, Tian C, Yu Y and Gao B: Molecular expression and functional analysis of genes in children with temporal lobe epilepsy. J Integr Neurosci 18: 71-77, 2019.
20. Han S, Wang WJ, Duan L, Hou ZL, Zeng JY, Li L, Meng MY, Zhang YY, Wang Y, Xie YH, *et al*: MicroRNA profiling of patients with sporadic atrial septal defect. Biotechnol Biotechnol Equip 33: 510-519, 2019.
21. Sánchez-Gómez MC, García-Mejía KA, Pérez-Díaz Conti M, Díaz-Rosas G, Palma-Lara I, Sánchez-Urbina R, Klünder-Klünder M, Botello-Flores JA, Balderrábano-Saucedo NA and Contreras-Ramos A: MicroRNAs association in the cardiac hypertrophy secondary to complex congenital heart disease in children. Pediatr Cardiol 38: 991-1003, 2017.
22. Xiao Y, Wang J, Chen Y, Zhou K, Wen J, Wang Y, Zhou Y, Pan W and Cai W: Up-regulation of miR-200b in biliary atresia patients accelerates proliferation and migration of hepatic stallate cells by activating PI3K/Akt signaling. Cell Signal 26: 925-932, 2014.
23. Shen W, Chen G, Dong R, Zhao R and Zheng S: MicroRNA-21/PTEN/Akt axis in the fibrogenesis of biliary atresia. J Pediatr Surg 49: 1738-1741, 2014.
24. Hand NJ, Horner AM, Master ZR, Boateng LA, LeGuen C, Uvaydova M and Friedman JR: MicroRNA profiling identifies miR-29 as a regulator of disease-associated pathways in experimental biliary atresia. J Pediatr Gastroenterol Nutr 54: 186-192, 2012.
25. Shen WJ, Dong R, Chen G and Zheng S: microRNA-222 modulates liver fibrosis in a murine model of biliary atresia. Biochem Biophys Res Commun 446: 155-159, 2014.
26. Xiao Y, Wang J, Yan W, Zhou Y, Chen Y, Zhou K, Wen J, Wang Y and Cai W: Dysregulated miR-124 and miR-200 expression contribute to cholangiocyte proliferation in the cholestatic liver by targeting IL-6/STAT3 signalling. J Hepatol 62: 889-896, 2015.
27. Yu DS, An FM, Gong BD, Xiang XG, Lin LY, Wang H and Xie Q: The regulatory role of microRNA-1187 in TNF-α-mediated hepatocyte apoptosis in acute liver failure. Int J Mol Med 29: 663-668, 2012.
28. An F, Gong B, Wang H, Yu D, Zhao G, Lin L, Tang W, Yu H, Bao S and Xie Q: miR-15b and miR-16 regulate TNF mediated hepatocyte apoptosis via BCL2 in acute liver failure. Apoptosis 17: 702-716, 2012.
29. Salehi S, Brereton HC, Arno MJ, Darling D, Quaglia A, O'Grady J, Heaton N and Aluvihare VR: Human liver regeneration is characterized by the coordinated expression of distinct microRNA governing cell cycle fate. Am J Transplant 13: 1282-1295, 2013.
30. Dattaroy D, Pourhoseini S, Das S, Alhasson F, Seth RK, Nagarkatti M, Michelotti GA, Diehl AM and Chatterjee S: Micro-RNA 21 inhibition of SMAD7 enhances fibrogenesis via leptin-mediated NADPH oxidase in experimental and human nonalcoholic steatohepatitis. Am J Physiol Gastrointest Liver Physiol 308: G298-G312, 2015.
31. Israelow B, Mullokandov G, Agudo J, Sourisseau M, Bashir A, Maldonado AY, Dar AC, Brown BD and Evans MJ: Hepatitis C virus genetics affects miR-122 requirements and response to miR-122 inhibitors. Nat Commun 5: 5408, 2014.
32. Karam RA and Abd Elrahman DM: Differential expression of miR-155 and Let-7a in the plasma of childhood asthma: Potential biomarkers for diagnosis and severity. Clin Biochem 68: 30-36, 2019.
33. Zhang Y, Sun E, Li X, Zhang M, Tang Z, He L and Lv K: miR-155 contributes to Df1-induced asthma by increasing the proliferative response of Th cells via CTLA-4 downregulation. Cell Immunol 314: 1-9, 2017.
34. Zhou Y, Yang Q, Xu H, Zhang J, Deng H, Gao H, Yang J, Zhao D and Liu F: miRNA-221-3p enhances the secretion of interleukin-4 in mast cells through the phosphatase and tensin homolog/p38/nuclear factor-kappaB pathway. PLoS One 11: e0148821, 2016.
35. Tsitsiou E, Williams AE, Moschos SA, Patel K, Rossios C, Jiang X, Adams OD, Macedo P, Booton R, Gibeon D, *et al*: Transcriptome analysis shows activation of circulating CD8+ T cells in patients with severe asthma. J Allergy Clin Immunol 129: 95-103, 2012.
36. Kärner J, Wawrzyniak M, Tankov S, Runnel T, Aints A, Kisand K, Altraja A, Kingo K, Akdis CA, Akdis M and Rebane A: Increased microRNA-323-3p in IL-22/IL-17-producing T cells and asthma: A role in the regulation of the TGF-β pathway and IL-22 production. Allergy 72: 55-65, 2017.
37. Liu F, Qin HB, Xu B, Zhou H and Zhao DY: Profiling of miRNAs in pediatric asthma: Upregulation of miRNA-221 and miRNA-485-3p. Mol Med Rep 6: 1178-1182, 2012.
38. Tian M, Zhou Y, Jia H, Zhu X and Cui Y: The clinical significance of changes in the expression levels of MicroRNA-1 and inflammatory factors in the peripheral blood of children with acute-stage asthma. Biomed Res Int 2018: 7632487, 2018.
39. Liang Y, Feng Y, Wu W, Chang C, Chen D, Chen S and Zhen G: microRNA-218-5p plays a protective role in eosinophilic airway inflammation via targeting δ-catenin, a novel catenin in asthma. Clin Exp Allergy 50: 29-40, 2020.
40. Ren L, Zhu R and Li X: Silencing miR-181a produces neuroprotection against hippocampus neuron cell apoptosis post-status epilepticus in a rat model and in children with temporal lobe epilepsy. Genet Mol Res 15, 2016.
41. Peng J, Omran A, Ashhab MU, Kong H, Gan N, He F and Yin F: Expression patterns of miR-124, miR-134, miR-132, and miR-21 in an immature rat model and children with mesial temporal lobe epilepsy. J Mol Neurosci 50: 291-297, 2013.

42. Risbud RM, Lee C and Porter BE: Neurotrophin-3 mRNA a putative target of miR21 following status epilepticus. Brain Res 1424: 53-59, 2011.
43. Li N, Pan J, Liu W, Li Y, Li F and Liu M: MicroRNA-15a-5p serves as a potential biomarker and regulates the viability and apoptosis of hippocampus neuron in children with temporal lobe epilepsy. Diagn Pathol 15: 46, 2020.
44. Achkar NP, Cambiagno DA and Manavella PA: miRNA biogenesis: A dynamic pathway. Trends Plant Sci 21: 1034-1044, 2016.
45. Kandhavelu M and Kandhavelu J: Pre-piRNA biogenesis mimics the pathway of miRNA. Biochem Syst Ecol 43: 200-204, 2012.
46. Murchison EP and Hannon GJ: miRNAs on the move: miRNA biogenesis and the RNAi machinery. Curr Opin Cell Biol 16: 223-229, 2004.
47. Saj A and Lai EC: Control of microRNA biogenesis and transcription by cell signaling pathways. Curr Opin Genet Dev 21: 504-510, 2011.
48. Suzuki HI and Miyazono K: Dynamics of microRNA biogenesis: Crosstalk between p53 network and microRNA processing pathway. J Mol Med (Berl) 88: 1085-1094, 2010.
49. Winter J, Jung S, Keller S, Gregory RI and Diederichs S: Many roads to maturity: microRNA biogenesis pathways and their regulation. Nat Cell Biol 11: 228-234, 2009.
50. American Diabetes Association: 2. Classification and diagnosis of diabetes. Diabetes Care 38 (Suppl 1): S8-S16, 2015.
51. American Diabetes Association: Diagnosis and classification of diabetes mellitus. Diabetes Care 37 (Suppl 1): S81-S90, 2014.
52. Tuomi T, Santoro N, Caprio S, Cai M, Weng J and Groop L: The many faces of diabetes: A disease with increasing heterogeneity. Lancet 383: 1084-1094, 2014.
53. Ma RCW: Epidemiology of diabetes and diabetic complications in China. Diabetologia 61: 1249-1260, 2018.
54. Moheet A, Mangia S and Seaquist ER: Impact of diabetes on cognitive function and brain structure. In: Year in Diabetes and Obesity. Powers AC and Ahima RS (eds). pp60-71, 2015.
55. Baroukh N, Ravier MA, Loder MK, Hill EV, Bounacer A, Scharfmann R, Rutter GA and Van Obberghen E: MicroRNA-124a regulates Foxa2 expression and intracellular signaling in pancreatic beta-cell lines. J Biol Chem 282: 19575-19588, 2007.
56. Keller DM, Clark EA and Goodman RH: Regulation of microRNA-375 by cAMP in pancreatic β-cells. Mol Endocrinol 26: 989-999, 2012.
57. Poy MN, Hausser J, Trajkovski M, Braun M, Collins S, Rorsman P, Zavolan M and Stoffel M: miR-375 maintains normal pancreatic alpha- and beta-cell mass. Proc Natl Acad Sci USA 106: 5813-5818, 2009.
58. Regazzi R: MicroRNAs as therapeutic targets for the treatment of diabetes mellitus and its complications. Expert Opin Ther Targets 22: 153-160, 2018.
59. Sun LL, Jiang BG, Li WT, Zou JJ, Shi YQ and Liu ZM: MicroRNA-15a positively regulates insulin synthesis by inhibiting uncoupling protein-2 expression. Diabetes Res Clin Pract 91: 94-100, 2011.
60. Shen Z, Yu Y, Yang Y, Xiao X, Sun T, Chang X, Tang W, Zhu Y and Han X: miR-25 and miR-92b regulate insulin biosynthesis and pancreatic β-cell apoptosis. Endocrine 76: 526-535, 2022.
61. Poy MN, Eliasson L, Krutzfeldt J, Kuwajima S, Ma X, Macdonald PE, Pfeffer S, Tuschl T, Rajewsky N, Rorsman P and Stoffel M: A pancreatic islet-specific microRNA regulates insulin secretion. Nature 432: 226-230, 2004.
62. Corno AF, Koerner TS and Salazar JD: Innovative treatments for congenital heart defects. World J Pediatr 19: 1-6, 2023.
63. Wu Y, Ma XJ, Wang HJ, Li WC, Chen L, Ma D and Huang GY: Expression of Cx43-related microRNAs in patients with tetralogy of Fallot. World J Pediatr 10: 138-144, 2014.
64. Dueñas A, Exposit A, Aranega A and Franco D: The role of non-coding RNA in congenital heart diseases. J Cardiovasc Dev Dis 6: 15, 2019.
65. Gu H, Chen L, Xue J, Huang T, Wei X, Liu D, Ma W, Cao S and Yuan Z: Expression profile of maternal circulating microRNAs as non-invasive biomarkers for prenatal diagnosis of congenital heart defects. Biomed Pharmacother 109: 823-830, 2019.
66. Hoelscher SC, Doppler SA, Dreßen M, Lahm H, Lange R and Krane M: MicroRNAs: Pleiotropic players in congenital heart disease and regeneration. J Thorac Dis 9 (Suppl 1): S64-S81, 2017.
67. Kalayinia S, Arjmand F, Maleki M, Malakootian M and Singh CP: MicroRNAs: Roles in cardiovascular development and disease. Cardiovasc Pathol 50: 107296, 2021.
68. Arabian M, Mirzadeh Azad F, Maleki M and Malakootian M: Insights into role of microRNAs in cardiac development, cardiac diseases, and developing novel therapies. Iran J Basic Med Sci 23: 961-969, 2020.
69. Paul S, Ruiz-Manriquez LM, Ledesma-Pacheco SJ, Benavides-Aguilar JA, Torres-Copado A, Morales-Rodríguez JI, De Donato M and Srivastava A: Roles of microRNAs in chronic pediatric diseases and their use as potential biomarkers: A review. Arch Biochem Biophys 699: 108763, 2021.
70. Smith T, Rajakaruna C, Caputo M and Emanueli C: MicroRNAs in congenital heart disease. Ann Transl Med 3: 333, 2015.
71. Tian J, An X and Niu L: Role of microRNAs in cardiac development and disease. Exp Ther Med 13: 3-8, 2017.
72. Xie WQ, Zhou L, Chen Y and Ni B: Circulating microRNAs as potential biomarkers for diagnosis of congenital heart defects. World J Emerg Med 7: 85-89, 2016.
73. Yan HL and Hua YM: Research advances on role of microRNAs in congenital heart diseases. Zhongguo Dang Dai Er Ke Za Zhi 16: 1070-1074, 2014 (In Chinese).
74. Zajkowska A and Małecki M: microRNAs role in heart development. Postepy Biol Komorki 42: 107-126, 2015.
75. Wei Y, Peng S, Wu M, Sachidanandam R, Tu Z, Zhang S, Falce C, Sobie EA, Lebeche D and Zhao Y: Multifaceted roles of miR-1s in repressing the fetal gene program in the heart. Cell Res 24: 278-292, 2014.
76. Xin M, Olson EN and Bassel-Duby R: Mending broken hearts: Cardiac development as a basis for adult heart regeneration and repair. Nat Rev Mol Cell Biol 14: 529-541, 2013.
77. Bruneau BG: The developmental genetics of congenital heart disease. Nature 451: 943-948, 2008.
78. Ho PTB, Clark IM and Le LTT: MicroRNA-based diagnosis and therapy. Int J Mol Sci 23: 7167, 2022.
79. Yu Z, Han S, Hu P, Zhu C, Wang X, Qian L and Guo X: Potential role of maternal serum microRNAs as a biomarker for fetal congenital heart defects. Med Hypotheses 76: 424-426, 2011.
80. Zhu S, Cao L, Zhu J, Kong L, Jin J, Qian L, Zhu C, Hu X, Li M, Guo X, *et al*: Identification of maternal serum microRNAs as novel non-invasive biomarkers for prenatal detection of fetal congenital heart defects. Clin Chim Acta 424: 66-72, 2013.
81. Della Corte C, Mosca A, Vania A, Alterio A, Alisi A and Nobili V: Pediatric liver diseases: Current challenges and future perspectives. Expert Rev Gastroenterol Hepatol 10: 255-265, 2016.
82. Calvopina DA, Coleman MA, Lewindon PJ and Ramm GA: Function and regulation of MicroRNAs and their potential as biomarkers in paediatric liver disease. Int J Mol Sci 17: 1795, 2016.
83. Makri E, Goulas A and Polyzos SA: Epidemiology, pathogenesis, diagnosis and emerging treatment of nonalcoholic fatty liver disease. Arch Med Res 52: 25-37, 2021.
84. Gheorghe G, Bungău S, Ceobanu G, Ilie M, Bacalbaşa N, Bratu OG, Vesa CM, Găman MA and Diaconu CC: The non-invasive assessment of hepatic fibrosis. J Formos Med Assoc 120: 794-803, 2021.
85. Tadokoro T, Morishita A and Masaki T: Diagnosis and therapeutic management of liver fibrosis by MicroRNA. Int J Mol Sci 22: 8139, 2021.
86. Wang X, He Y, Mackowiak B and Gao B: MicroRNAs as regulators, biomarkers and therapeutic targets in liver diseases. Gut 70: 784-795, 2021.
87. Hartley JL, Davenport M and Kelly DA: Biliary atresia. Lancet 374: 1704-1713, 2009.
88. Bezerra JA, Wells RG, Mack CL, Karpen SJ, Hoofnagle JH, Doo E and Sokol RJ: Biliary atresia: Clinical and research challenges for the twenty-first century. Hepatology 68: 1163-1173, 2018.
89. Sokol RJ, Shepherd RW, Superina R, Bezerra JA, Robuck P and Hoofnagle JH: Screening and outcomes in biliary atresia: Summary of a national institutes of health workshop. Hepatology 46: 566-581, 2007.
90. Balasubramaniyan N, Devereaux MW, Orlicky DJ, Sokol RJ and Suchy FJ: Up-regulation of miR-let7a-5p leads to decreased expression of ABCC2 in obstructive cholestasis. Hepatol Commun 3: 1674-1686, 2019.
91. Zhao R, Dong R, Yang Y, Wang Y, Ma J, Wang J, Li H and Zheng S: MicroRNA-155 modulates bile duct inflammation by targeting the suppressor of cytokine signaling 1 in biliary atresia. Pediatr Res 82: 1007-1016, 2017.

92. Dong R, Zheng Y, Chen G, Zhao R, Zhou Z and Zheng S: miR-222 overexpression may contribute to liver fibrosis in biliary atresia by targeting PPP2R2A. J Pediatr Gastroenterol Nutr 60: 84-90, 2015.
93. Zhao D, Luo Y, Xia Y, Zhang JJ and Xia Q: MicroRNA-19b expression in human biliary atresia specimens and its role in BA-related fibrosis. Dig Dis Sci 62: 689-698, 2017.
94. Yoneyama T, Ueno T, Masahata K, Toyama C, Maeda A, Tazuke Y, Oue T, Miyagawa S and Okuyama H: Elevation of microRNA-214 is associated with progression of liver fibrosis in patients with biliary atresia. Pediatr Surg Int 38: 115-122, 2022.
95. Chang J, Liang J, Chai C, Liu F, Tao B, Wang H, Tong Y, Wang Z and Xia H: MiR-100 rs1834306 A>G increases biliary atresia risk in Southern Han Chinese children. Biomed Res Int 2023: 4835839, 2023.
96. Su L, Tian Y, Fu M, Zhang RZ, Ou XF, Xia HM and Li RZ: Association of miRNA-492 rs2289030 G>C and miRNA-938 rs2505901 T>C gene polymorphisms with biliary atresia susceptibility. Biomed Environ Sci 34: 577-580, 2021.
97. Shan Y, Shen N, Han L, Chen Q, Zhang J, Long X and Xia Q: MicroRNA-499 Rs3746444 polymorphism and biliary atresia. Dig Liver Dis 48: 423-428, 2016.
98. Cook NL, Pereira TN, Lewindon PJ, Shepherd RW and Ramm GA: Circulating microRNAs as noninvasive diagnostic biomarkers of liver disease in children with cystic fibrosis. J Pediatr Gastroenterol Nutr 60: 247-254, 2015.
99. Boonpiyathad T, Sözener ZC, Satitsuksanoa P and Akdis CA: Immunologic mechanisms in asthma. Semin Immunol 46: 101333, 2019.
100. Papi A, Brightling C, Pedersen SE and Reddel HK: Asthma. Lancet 391: 783-800, 2018.
101. Liang J, Liu XH, Chen XM, Song XL, Li W and Huang Y: Emerging roles of non-coding RNAs in childhood asthma. Front Pharmacol 13: 856104, 2022.
102. Kai W, Qian XU and Qun WUZ: MicroRNAs and asthma regulation. Iran J Allergy Asthma Immunol 14: 120-125, 2015.
103. Midyat L, Gulen F, Karaca E, Ozkinay F, Tanac R, Demir E, Cogulu O, Aslan A, Ozkinay C, Onay H and Atasever M: MicroRNA expression profiling in children with different asthma phenotypes. Pediatr Pulmonol 51: 582-587, 2016.
104. Mousavi SR, Ahmadi A, Jamalkandi SA and Salimian J: Involvement of microRNAs in physiological and pathological processes in asthma. J Cell Physiol 234: 21547-21559, 2019.
105. Jat KR and Kabra SK: Awareness about childhood asthma. Indian J Med Res 145: 581-583, 2017.
106. Foster PS, Maltby S, Rosenberg HF, Tay HL, Hogan SP, Collison AM, Yang M, Kaiko GE, Hansbro PM, Kumar RK and Mattes J: Modeling T_H 2 responses and airway inflammation to understand fundamental mechanisms regulating the pathogenesis of asthma. Immunol Rev 278: 20-40, 2017.
107. Specjalski K and Niedoszytko M: MicroRNAs: Future biomarkers and targets of therapy in asthma? Curr Opin Pulm Med 26: 285-292, 2020.
108. van den Berge M and Tasena H: Role of microRNAs and exosomes in asthma. Curr Opin Pulm Med 25: 87-93, 2019.
109. Cañas JA, Rodrigo-Muñoz JM, Sastre B, Gil-Martinez M, Redondo N and Del Pozo V: MicroRNAs as potential regulators of immune response networks in asthma and chronic obstructive pulmonary disease. Front Immunol 11: 608666, 2021.
110. Xu L, Yi M, Tan Y, Yi Z and Zhang Y: A comprehensive analysis of microRNAs as diagnostic biomarkers for asthma. Ther Adv Respir Dis 14: 1753466620981863, 2020.
111. Chiba Y: Non-coding RNAs and bronchial smooth muscle hyperresponsiveness in allergic bronchial asthma. Nihon Yakurigaku Zasshi 155: 364-368, 2020 (In Japanese).
112. Lukiw WJ: Circular RNA (circRNA) in Alzheimer's disease (AD). Front Genet 4: 307, 2013.
113. He X, Jing Z and Cheng G: MicroRNAs: New regulators of Toll-like receptor signalling pathways. Biomed Res Int 2014: 945169, 2014.
114. Katyayan A and Diaz-Medina G: Epilepsy: Epileptic syndromes and treatment. Neurol Clin 39: 779-795, 2021.
115. Paul S, Reyes PR, Garza BS and Sharma A: MicroRNAs and child neuropsychiatric disorders: A brief review. Neurochem Res 45: 232-240, 2020.
116. Ma Y: The challenge of microRNA as a biomarker of epilepsy. Curr Neuropharmacol 16: 37-42, 2018.
117. Brennan GP and Henshall DC: microRNAs in the pathophysiology of epilepsy. Neurosci Lett 667: 47-52, 2018.
118. Cava C, Manna I, Gambardella A, Bertoli G and Castiglioni I: Potential role of miRNAs as theranostic biomarkers of epilepsy. Mol Ther Nucleic Acids 13: 275-290, 2018.
119. Ghafouri-Fard S, Hussen BM, Abak A, Taheri M and Jalili Khoshnoud R: Aberrant expression of miRNAs in epilepsy. Mol Biol Rep 49: 5057-5074, 2022.
120. van der Lee JH, Mokkink LB, Grootenhuis MA, Heymans HS and Offringa M: Definitions and measurement of chronic health conditions in childhood: A systematic review. JAMA 297: 2741-2751, 2007.
121. Diener C, Keller A and Meese E: Emerging concepts of miRNA therapeutics: From cells to clinic. Trends Genet 38: 613-626, 2022.
122. Groot M and Lee H: Sorting mechanisms for MicroRNAs into extracellular vesicles and their associated diseases. Cells 9: 1044, 2020.
123. Laggerbauer B and Engelhardt S: MicroRNAs as therapeutic targets in cardiovascular disease. J Clin Invest 132: e159179, 2022.
124. Vegter EL, van der Meer P, de Windt LJ, Pinto YM and Voors AA: MicroRNAs in heart failure: From biomarker to target for therapy. Eur J Heart Fail 18: 457-468, 2016.