

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

1. Introduction
2. MicroRNA biogenesis pathway
3. MicroRNAs in diabetes mellitus
4. MicroRNAs in CHD
5. MicroRNAs in liver diseases
6. MicroRNAs in bronchial asthma

7. MicroRNAs in epilepsy
8. Conclusion

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).

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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

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

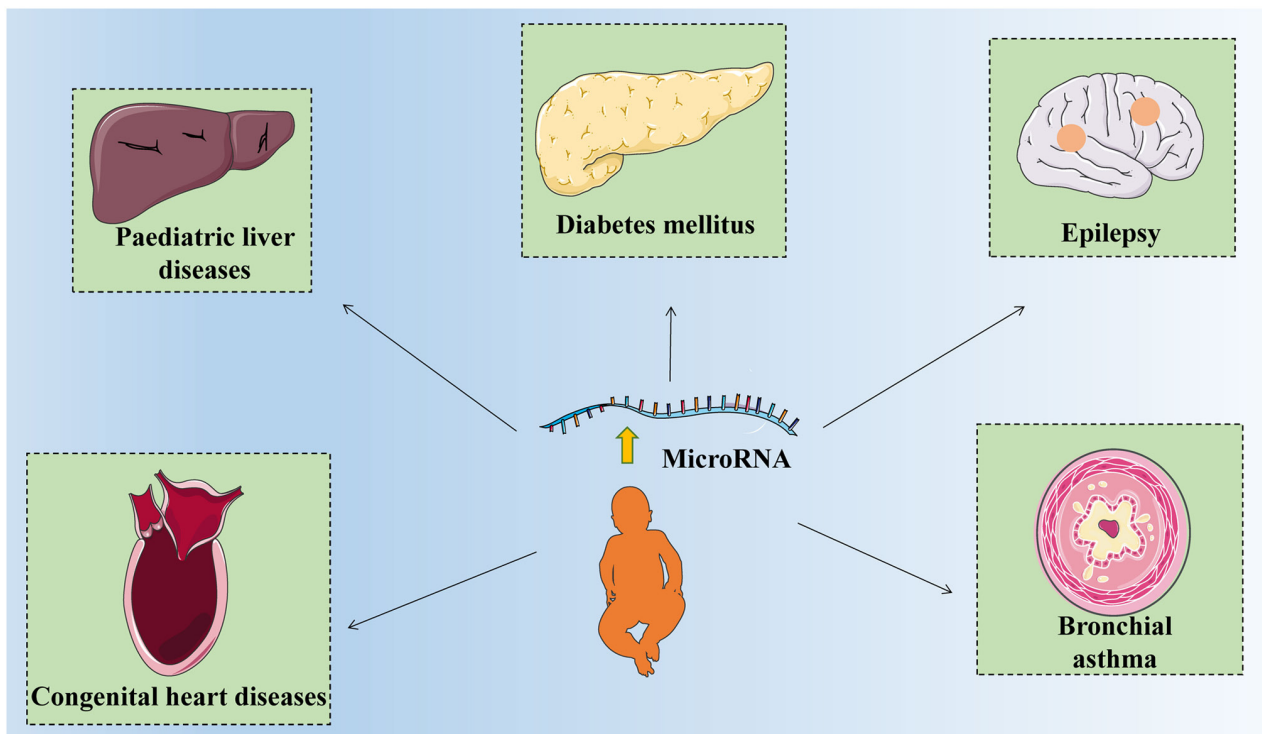


Figure 1. MicroRNAs serve roles in diabetes mellitus, congenital heart diseases, liver diseases, bronchial asthma and epilepsy in children, and therefore may be used as promising biomarkers for the diagnosis and treatment of chronic pediatric diseases.

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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MZ and YH reviewed the literature and wrote the manuscript. Both authors have read and approved the final manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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