The Potential Role of Micro-RNA`s in Pediatric Disease Pathogenesis

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Abstract: MicroRNAs are short, highly conserved, non-coding ribonucleic acids that play an important role in the complex network of gene regulation, especially in gene silencing. MicroRNAs regulate gene expression highly specifically at the post-transcriptional level. MicroRNAs have a size of 21 to 23 nucleotides, but there can be even a few hundred. In recent years, knowledge about microRNAs has steadily grown. The miR Base database has shown an increase of over 4000 sequences within few years and, each miRNA has the potential to target a large number of genes. Why the database of new miRNAs is rising, is not completely understood to date. Working with miRNAs is at the forefront of biomedical research. Since their discovery in 1993, significant knowledge about miRNAs has been gathered: their biogenesis has been elucidated, the components involved in RNA interference have been identified, and insight into the therapeutic importance of miRNAs has been gained - both as drugs and as targets for new therapies. Further intensive research will help identify the key molecular players in this miRNA-mediated signaling pathway and understand their function. Strategies are being developed to influence the activity of these proteins, in order to draw conclusions from these experiments about their respective functions. This will certainly help develop new therapeutic approaches for the treatment of human diseases that can be attributed to RNA interference dysfunctions. The exact biological functions of most microRNAs are still unknown. According to computer-based predictions, approximately 20-30% of genes in the human genome could be regulated by microRNAs. It is assumed that several thousand different microRNAs are encoded. Micro-RNA`s play an important role in pathogenesis of many different pediatric diseases, which will be analyzed in this review in detail.

Keywords: Micro RNA, Nucleotides, Translation, Genome, Child.

INTRODUCTION

Transcription and function are described using mammals as an example. With variations, such as the involved protein components, the mechanism of action is comparable in different species. The genes for miRNAs are located in the genome and are transcribed by RNA polymerase II or III. The resulting primary transcript is 500 to 3000 nucleotides long and carries the usual poly-A tail at the 3' end and a 7-methylguanosine cap at the 5' end. The primary transcript is called primary microRNA (pri-miRNA) and folds into a loop. The RNase III (Drosha) and the dsRNA-binding protein DGCR8 (corresponding to Pasha in Drosophila melanogaster) form a microprocessor complex, which processes the pri-miRNA in the cell nucleus into a precursor microRNA (pre-miRNA) of about 70-80 nucleotides. The pre-miRNA forms a characteristic hairpin structure. The pre-miRNA is exported to the cytoplasm by Exportin-5 in the presence of Ran-GTP as a cofactor through the nuclear pores of the nuclear membrane. In the cytoplasm, the pre-miRNAs are cleaved into 17-24 nt long ds-miRNAs by the RNAse III enzyme Dicer. Dicer interacts with the dsRNA-binding protein TRBP (RDE-4 in C. elegans and Loquacious in Drosophila melanogaster). Dicer loads the still double-stranded miRNA onto a protein called Argonaut 2 (AGO2), forming the RNA-induced silencing complex-loading complex, consisting of Dicer, TRBP, and AGO2. AGO2 removes one strand, the passenger strand, and forms the RNA-induced silencing complex (miRISC) with the miRNA guide strand. Once RISC is formed, it locates its target mRNA by searching for base sequence matches. For RISC or target mRNA interaction to occur, there must be complementarity of about 7 base pairs, with nucleotides 2-8, viewed from the 5' end of the miRNA, being particularly important. Higher complementarity improves binding. How AGO2 precisely selects the miRNA guide strand and knows which strand to degrade is still unclear. However, it is known that the selection is targeted. Two factors seem to play a particularly important role: first, the nucleobase at the 5'-end is crucial, with a preference for uracil. Second, the strand with a thermodynamically unstable 5'-end can be more easily taken up by RISC. Depending on this, the miRNA strand with the 5'-terminus at its end forms the mature miRNA, also called the guide RNA. The passenger strand is annotated with an asterisk. This miRNA* may

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potentially have regulatory effects in a few cases. The selection of mRNA to be degraded is based on complementarity with the miRNA. The more bases that are complementary between mRNA and miRNA, the better the translation repression works. Additionally, miRNAs preferentially bind to the 3'-UTR (untranslated region) of mRNA. When RISC docks at the 3' end of the mRNA, it has more time for translation repression, and time is a significant factor as mRNA is rapidly translated in the cytosol. The mature miRNA is incorporated into a ribonucleoprotein complex (miRNP), which bears a strong resemblance to the RISC complex of the RNAi pathway. Through this miRISC complex, the activity of target genes can be downregulated by two methods. The mechanisms of action of microRNAs and small interfering RNAs (siRNAs) show clear parallels. siRNAs are processed by the RNase III Dicer from long double-stranded RNAs (dsRNAs) and taken up as 21-28 nt long single-stranded RNAs into the siRISC complex, which mediates mRNA degradation.

MECHANISM OF GENE REGULATION

In animals, gene regulation occurs through the binding of microRNAs to the 3' untranslated region (3'-UTR) of target gene mRNAs, which, depending on the complementarity of the binding sequence and the involved proteins, can either inhibit translation or lead to mRNA degradation. Essentially, RISC has three options to regulate gene expression: a) translation inhibition followed by mRNA degradation, b) inhibition without mRNA degradation, and c) direct mRNA degradation before translation initiation. Translation inhibition (variants a and b) is more common than direct mRNA strand degradation (variant c) because variants a and b require less complementarity with the target mRNA. The most widely accepted model for miRNA-mediated silencing is that translation inhibition occurs first, followed by mRNA degradation. In variant a, the mRNA-miRNA complementarity is not sufficient for AGO2 to degrade the mRNA on its own. Therefore, additional proteins must be recruited. The leading protein in this process is GW182, which recruits decapping and deadenylation factors. By removing the cap structure and poly(A) tail, the mRNA is destabilized. A third protein complex, XNR1, then degrades the mRNA in the 5'-3' direction. Variant b, translation inhibition without mRNA degradation, is more complex, and the detailed mechanisms require further experimental validation. One postulated mechanism involves two important initiation factors (eIF4E and eIF4G). They are inhibited by RISC and dissociate from the translation machinery. Without them, the small ribosomal subunit cannot bind to the 5'-cap structure, preventing mRNA translation. Variant a appears to be more common than b. Direct mRNA strand degradation by RISC is less common. For this to occur, the miRNA must be extensively, if not completely, complementary to the mRNA, which is uncommon in humans compared to plants. Most miRNAs have evolved to be imperfectly complementary to regulate more genes. It is a compromise between accuracy and efficiency. Another RNA class that regulates gene expression through RNAi is small interfering RNAs (siRNAs). Because miRNAs and siRNAs are processed similarly and have interchangeable biochemical functions, distinguishing between them is not straightforward. miRNAs originate from hairpin-like structures, while siRNAs come from long RNA templates (dsRNA) that can yield multiple siRNAs. Only one miRNA can be extracted from a hairpin structure, while siRNAs can target only one mRNA at a time, miRNAs often have multiple targets (an average of 200 mRNAs). This is due to the imperfect complementarity of miRNAs, allowing them to bind to an mRNA even if some bases are not complementary, which is not possible with siRNAs. While siRNAs induce irreversible mRNA degradation, miRNAs can temporarily suppress translation and dissociate when the protein is needed. Although microRNAs have received significant attention in research, a central mechanism is still poorly understood. MicroRNAs are generally considered negative regulators of gene expression. However, various review articles suggest that microRNAs can also stimulate translation. The exact mechanisms of how they do this are largely unknown in many cases. A study from 2007 demonstrated that a microRNA (miR-369-3), which normally suppresses translation, helped activate the cell cycle in cells whose cell cycle had been arrested. This microRNA formed an initiation complex, involving AGO2, which seemed responsible for mRNA degradation. This phenomenon was observed in the G0/G1 phase but not during cell proliferation. Other studies support the idea that microRNAs can stimulate gene expression. Some publications even suggest that stimulating gene expression is the main function of microRNAs. This is supported by the fact that gene expression decreased when AGO genes were knocked out, contradicting the widespread belief that microRNAs predominantly silence genes. MicroRNAs have diverse expression patterns and are regulated differently during

development and physiological processes. Expression is usually tissue-specific and organized along with nearby genes. MicroRNAs can be located within exons or introns of protein-coding genes or in non-coding regions. Some microRNAs have their own promoters, while a few microRNAs are clustered and transcribed together.

MicroRNAs are short RNA molecules that, unlike regular RNA strands, are not translated into proteins. Their function is to bind to other RNA molecules and thereby prevent their translation into proteins or even cause the degradation of the RNA molecules.

CURRENT RESEARCH

The study of microRNA is a new and very current topic in molecular and cell biology. Working with miRNAs is more challenging than with mRNAs because they are quickly degraded due to their small size and ubiquitous presence of degradation enzymes. Quantifying miRNA requires constant work under cooling conditions and specially prepared, RNase-free equipment. Traditionally, miRNA expression levels are studied by transcribing RNA into synthetic DNA (cDNA) and quantifying it using quantitative PCR. Recently, it has become possible to measure miRNA expression on specialized microarray platforms, a method that is gaining popularity. Although this allows for the simultaneous assessment of hundreds of miRNAs, data post-processing, as is typical with microarrays, is labor-intensive and often associated with significant variability. However, this can often be compensated for by analyzing datasets, which ideally include additional information on regulated mRNAs. In recent years, it has been found that miRNAs play a significant role in regulating gene translation after transcription. This occurs through specific binding to mRNA molecules, making translation into proteins more difficult, completely preventing it, or even facilitating it. In mammalian cells, over 800 different miRNAs have been identified so far, with over 1,800 different miRNA species known in humans, which are available in collections, so-called libraries. Comparing invertebrate and vertebrate cells shows that the structure of some of these molecules is highly conserved, indicating an important common evolutionary function in very different species. Experimental and computational studies suggest that each miRNA can regulate several mRNA molecules, and that 20-30% of all human genes are co-regulated by miRNAs. The type and number of miRNA molecules produced in the cell nucleus often show a close correlation with the cell's developmental stage (cell division, differentiation into specific cell types, apoptosis. miRNAs work in a regulatory network with transcription factors. Recent studies demonstrate the critical function of miRNAs in early animal developmental processes, such as neurogenesis, myogenesis, cardiogenesis, and hematopoiesis. miRNAs also play an important role in plants. It has also been suggested that miRNAs are crucial for suppressing cellular transformations such as tumor formation, as faulty miRNA molecule formation in cells enhances these unwanted processes. Deregulation of miRNAs has been observed in various types of tumors and seems to exhibit tumor-specific characteristics. The influence of the tumor suppressor protein p53 on the maturation of various miRNAs that inhibit cell growth also supports this conclusion. The potential role of miRNAs in the pathogenesis, diagnosis, and treatment of epilepsy has been highlighted. Changes in miRNA levels in patients with temporal lobe epilepsy and animal models have been identified. Functional studies have shown promising results, including the

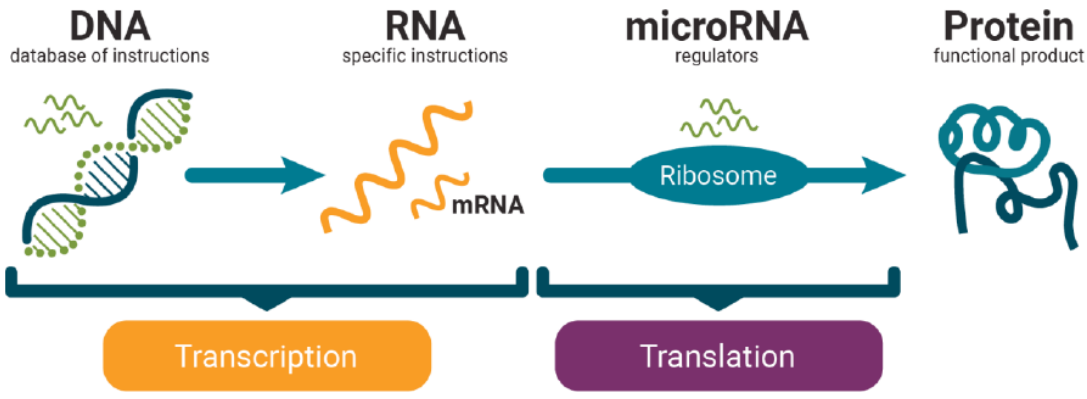

Figure 1: Development of microRNA and the role of transcriptional and translational process.

strong antiepileptic effects of suppressing brain-specific miR-134. Changes in miRNA expression have also been observed in other refractory epilepsy types, and understanding miRNA regulation, delivery methods, and diagnostic biomarker potential has expanded. Recent research indicates that certain miRNAs are essential for maintaining pluripotency and self-renewal of embryonic stem cells. Therefore, microRNAs could represent useful molecular tools for manipulating stem cells in the future. For research purposes, cellular microRNA molecules can be inhibited using complementary antagomirs.

The presence of specific microRNAs may also be used for diagnosing diseases such as myocarditis.

Recent findings suggest that miRNA can be ingested through diet and influence processes in the body. The base sequences of different miRNAs are identical or nearly identical in mammals. These similarities can be verified online through database queries. At the same time, there is organ specificity in all species, so that identical miRNA types in the same organs of different mammals perform their functions in the context of modulating protein biosynthesis. Important microRNAs in the human cell MicroRNA-335(-5p), whose transcript template is located in the gene sequence for MEST, has been identified as an important regulator in the development of malignant tumors but also recognized as an oncogenic oncomir. In 2005, Chan and colleagues discovered that miR21 was highly overexpressed in cells of glioblastomas. miR21 has also been found in numerous other tumors, such as breast cancer, colorectal cancer, lung cancer, pancreatic cancer, prostate cancer, liver cancer, gastric cancer, ovarian cancer, cervical cancer, head and neck tumors, leukemias, and others. In non-small cell lung cancer (NSCLC) cell lines, inhibiting miR21 with an antibody reduced tumor cell growth, migration, and invasion. Resistance to ionizing radiation and chemotherapeutics was increased by miR21. The expression of PTEN, a crucial signaling molecule in apoptosis, was increased by anti-miR21. This means that tumor cells overexpressing miR21 are protected from apoptosis. The importance of miR21 for the hematopoietic system was studied in miR21 knockout mice, where the gene for miR21 synthesis was switched off. It was found that the sensitivity to whole-body irradiation was increased by miR21 knockout. The impairment of hematopoietic stem and progenitor cells was identified as the cause, leading to bone marrow insufficiency. MiR-193b is regulated by STAT5 and modulates the expression of KIT, a receptor tyrosine kinase important for blood stem cells. It is involved in the renewal and expansion of blood stem cells and progenitor cells (blood precursor cells). Dysregulation of miR-193b is linked to the pathogenesis and aggressiveness of acute myeloid leukemia (AML). MicroRNA-145 reduces the expression of Oct-4, a stem cell-specific gene. Its loss promotes the formation of cancer stem cells. The microRNAs of the miR-302 family are typical for human embryonic stem cells and are regulated by the pluripotency genes Oct-4 and Sox-2.

CHRONOBIOLOGY, NAMING AND NOMENCLATURE OF MicroRNA‘s

In 2021, it was discovered that microRNA plays a crucial role in setting the period lengths in chronobiology. Both the amount of microRNA and the tissue type (lung, brain, retina) are important. The naming of microRNAs follows the temporal order of sequencing. The first three letters denote the organism. Different precursor sequences and genomic loci that express identical mature sequences are named in the form hsa-mir-121-1 and hsa-mir-121-2. Suffixes denoted by letters name closely related mature sequences – for example, hsa-miR-121a and miR-hsa-121b. miRNA cloning studies sometimes identify two approximately 22-base sequences originating from the same predicted precursor. If the relative quantities clearly indicate which is the predominant miRNA form, the mature sequences are assigned names like miR-56 (main product) and miR-56* (from the opposite arm of the precursor). If the data are insufficient to determine which sequence is predominant, names like miR-142-5p (from the 5'-arm) and miR-142-3p (from the 3'-arm) are given. An older convention that is sometimes used is, for example, miR-142 and miR-s-142-AS.

MicroRNA‘s as Biomarkers

The exact mechanisms of release and the function of extracellular miRNAs are not yet fully understood, but the data suggest that circulating miRNAs can be taken up by other cells, making them part of a new type of cell-cell communication system [33, 41]. The fact that miRNAs are released into the blood can be used to obtain information about cellular and tissue functions, especially damage to specific cell types, based on changes in miRNA profiles in the blood. MiRNAs have several important advantages for use as biomarkers: high stability in frozen samples for retrospective analysis; easy, scalable, and rapid detection with established methods for the detection and quantification of nucleic acids like quantitative PCR and

next generation sequencing; detection in easily accessible biofluids such as plasma, serum, urine, saliva, and tears and high tissue specificity of individual miRNAs allows for determination of the origin of circulating miRNAs and thus cell type-specific detection of tissue damage [33, 41, 55, 57, 60].

POTENTIAL ROLE OF MicroRNA's IN PEDIATRIC DISEASE PATHOGENESIS

MicroRNA and Pediatric Cancer

Micro RNA`s seem to play an important molecular role in the pathogenesis of childhood tumors with and incidence of 400000 children from age 0-19 per year [1, 13-15, 19, 22, 24, 31, 35, 37, 42, 44, 56, 58, 61]. Central nervous system tumors pose a significant challenge in modern medicine due to their location. The role of microRNA in the development of cancerous changes is crucial. The presence of miRNA was first described in the 1990s, and its significance has been recognized in various medical conditions including kidney disease, diabetes, neurodegenerative disorders, arthritis, and cancer. Several miRNAs are involved in processes such as invasiveness, apoptosis, treatment resistance, angiogenesis, proliferation, and immunology. Recent research on gliomas has highlighted the important role of miRNA in cancer development, influencing proliferation, angiogenesis, apoptosis regulation, and resistance to chemotherapy [1]. Moreover, microRNA`s seem to play an important role in neuroblastoma, glioblastoma and rhabdo-myosarcoma pathogenesis in childhood [37, 42, 61].

MicroRNAs are Key Players in Leukemia Pathogenesis

MicroRNAs are key players in leukemia pathogenesis (most common accounting for 1 of 3 cases with cancer), with altered expression linked to various cancers [2, 20, 40, 45, 54]. In a study of 70 pediatric acute lymphoblastic leukemia (ALL) patients, miR-128 levels were significantly higher compared to healthy controls ($p<0.001$), while let-7b levels showed no significant difference [2]. Clinical details, lab data, and treatment response did not correlate with miRNA expression. These findings suggest miR-128 as a potential diagnostic and prognostic marker for childhood ALL, warranting further investigation of let-7b's role in the disease [2].

MicroRNAs and Pediatric Diabetes Type 1

Type 1 diabetes mellitus (T1DM), with an increased mortality of 7-40 per cent, is a complex metabolic disorder characterized by hyperglycemia, increasingly affecting children and adolescents. There is a prevalence of 9.5 per cent snd 15/100000 people get be diagnosed by the disease. Recent research has identified microRNAs (miRNAs) as potential biomarkers for T1DM diagnosis [3, 21]. This review summarizes the role of miRNAs in T1DM pathogenesis, highlighting their biosynthesis, action pathways, and regulatory functions in gene expression. MiRNAs undergo a complex biosynthesis process involving cleavage and transport from the nucleus to the cytoplasm. Once assembled, they inhibit translation or degrade messenger RNA (mRNA), disrupting protein synthesis. Studies have shown that miRNAs play a crucial role in T1DM by affecting pancreatic β-cell function, insulin production, and secretion, leading to β-cell destruction and the production of autoreactive agents. The elevated levels of miRNAs in biological samples and their involvement in T1DM pathogenesis suggest their potential as early diagnostic biomarkers [3, 21]. Further research is needed to explore their diagnostic value in preclinical T1DM detection [3, 21].

MicroRNAs and Inflammasomopathies in Childhood

MicroRNAs are small non-coding RNA sequences that regulate gene expression post-transcriptionally. They play a crucial role in controlling inflammatory responses by modulating immune cell proliferation and activation [4, 25, 30, 32, 36, 48, 52]. Dysregulation of miRNA expression is observed in various immune-mediated inflammatory disorders, including autoinflammatory diseases (AID). AID are rare hereditary disorders characterized by abnormal activation of the innate immune system, leading to recurrent fevers. Inflammasomopathies, a major subgroup of AID, are linked to genetic defects in inflammasome activation, which regulates the maturation of IL-1 family cytokines and pyroptosis. The role of miRNAs in AID, particularly inflammasomopathies, is a growing area of research with limited current understanding. This review provides an overview of AID, inflammasomopathies, and the emerging role of miRNAs in these disease processes. Different forms of otitis media in childhood were related to the expression of microRNA`s [36]. In a study conducted at Bukovinian State Medical University and the Centre of Reproductive Medicine, 30 infertile women were involved [65]. The control group comprised 10 women with tubal infertility due to prior inflammation, who were deemed healthy after thorough clinical and laboratory evaluations. The control group, aged 21-42 years with an average age of 29.75 years,

did not receive the probiotic Femina Probiz [65]. The main group included 20 women with external genital endometriosis undergoing assisted reproductive technologies, who were given the probiotic Femina Probiz [65]. They took one tablet containing 10×10^9 Lactobacillus organisms twice daily for one month before the assisted reproductive technologies. NLRP3 inflammasome levels were measured before and after this treatment phase. The main group had a significantly higher incidence of primary infertility [65]. Micro RNAs inflammosome levels can therefore be used for the incidence of primary infertility, also possibly in women with thyroid autoimmunity [63, 64].

MicroRNA`s as Biomarker for Kawasaki Disease

Kawasaki disease has an incidence of 3.1/1000000/year in children under 17 years. In a recent study, next-generation sequencing identifies micro-RNA-based biomarker panel for Kawasaki disease [5]. In this study, 37 FC and 31 KD subjects were selected based on specific criteria for further validation with qPCR. Researchers identified 10 miRNAs with high abundance in NGS data and significant fold change between FC and KD libraries [5]. The qPCR results for these miRNAs were consistent with NGS data, with 8 showing significant differential expression. While 2 miRNAs were not statistically significant, the expression trends were still noticeable. Given the higher incidence of KD in males, we examined if the 10 miRNAs showed sex-specific expression [5]. Only hsa-miR-941 had a significant difference between males and females, but the difference between control and disease groups was more pronounced [5]. The other 9 miRNAs did not show sex-specific expression. Using the DCt values of these miRNAs, researchers developed a KD biomarker panel and trained a SVM classification model for diagnosis [5].

MicroRNA`s and Pediatric Metabolic Diseases

Metabolic diseases, such as diabetes mellitus, obesity, metabolic syndrome, and non-alcoholic fatty liver disease (NAFLD), are significant health concerns [6, 27]. Circular RNA, a unique type of RNA with a closed loop structure, has emerged as a novel area of research in understanding metabolic diseases. However, the role of circular RNA in these conditions is not fully understood, with limited studies exploring its association with DM and NAFLD [6, 27]. This chapter reviews the epidemiology, pathophysiology, and treatment of DM and NAFLD before delving into the current understanding of circular RNA's involvement in these diseases. Additionally, it discusses recent advancements in circular RNA research and its potential applications in molecular diagnostics, nucleic acid therapy, and biomarker development [6, 27].

MicroRNA`s and Hirschsprung Disease

On the 100th anniversary of Dr. Harald Hirschsprung's death, global research is focused on understanding the genetic and biochemical factors involved in Hirschsprung disease (HSCR) and developing new therapies [7, 51]. The incidence in HD is 1:4000 births. HSCR, also known as aganglionic megacolon, is a common challenge in perinatology and pediatric surgery, causing neonatal intestinal obstruction due to the absence of enteric nervous system ganglia. A recent review discusses the genes and pathways associated with HSCR, including the role of microRNAs in its pathogenesis [7, 51]. While HSCR is often sporadic, some cases show Mendelian inheritance patterns. Recent studies suggest that gene modules with common functions may contribute to HSCR across different populations. This information can guide future research on the complex nature of HSCR [7, 51].

MicroRNA`s and Hypoplastic Heart Disease

Micro-RNAs (miRNAs) play a crucial role in regulating gene expression by interacting with the 3'UTR of target messenger RNAs. The incidence is 1/3500 to 1/12500 live births. A recent study focused on analyzing the miRNA profile in patients with hypoplastic left heart syndrome (HLHS), a common and severe congenital heart disease in infants and children [8, 18, 47]. The miRNA profile in the right ventricle of HLHS patients was determined using miRNA array and validated through reverse-transcription polymerase chain reaction. Bioinformatics analysis was conducted to select targets, and their expression was analyzed using RT-PCR. The study revealed a unique miRNA profile in HLHS patients, distinct from pediatric and adult idiopathic dilated cardiomyopathy [8, 18, 47]. The identified miRNAs target genes crucial for cardiac development and disease, showing an inverse regulation pattern. Additionally, miRNA expression was found to change with the stage of surgery, indicating the impact of ventricle volume unloading on gene expression. The study suggests a specific miRNA profile associated with cardiac development and disease in HLHS patients [8, 18, 47].

MicroRNA`s and Subacute Sclerosing Panencephalitis (SSPE)

Subacute sclerosing panencephalitis (SSPE) is a progressive neurodegenerative disease caused by a persistent infection of defective measles virus in children and young adults [9, 39]. In the United states, onle 4-5 cases will be diagnosed yearly. Interferon-lambdas (IFN-λs) are cytokines that play a role in antiviral responses, with IL-29 levels being significantly higher in cells infected with defective measles virus. A recent study aimed to investigate the contribution of IL-28B, IL-29 levels, and gene polymorphisms to the immune response in SSPE, as well as the association of the miR-548 family with IL-29 and SSPE [9, 39]. We analyzed 64 SSPE patients and 68 healthy controls for rs12979860, rs8099917, rs30461 frequencies, serum IL-28B, IL-29 levels, and miR-548b, miR-548c, miR-548i expression levels [9, 39]. Results showed significantly higher serum IL-29 levels in SSPE patients, with the rs8099917 G allele increasing the risk of SSPE by 2.183-fold. Expression levels of miR-548b-5p, miR-548c-5p, and miR-548i were also higher in SSPE patients [9, 39]. The elevated IL-29 levels suggest a compensatory response to an over-activated immune system. Further studies on IL28, IL29, and related miRNAs may provide insights into the pathogenesis of SSPE in childhood [9, 39].

MicroRNA`s and Allergic Disease

MicroRNAs are short, single-stranded, non-coding RNAs that play a crucial role as epigenetic regulators in various diseases such as cancer, cardiovascular diseases, connective tissue diseases, and neuromuscular disorders [10]. Recent research has identified key miRNAs, including let-7, miR-21, miR-142, and miR-146, that are central to allergic inflammation [10, 27-29, 62]. A former review consolidates recent findings on the role of miRNAs in regulating allergic inflammation, focusing on conditions like asthma, atopic dermatitis, allergic rhinitis, and eosinophilic esophagitis [10, 27-29, 62]. Additionally, a discussion of extracellular miRNAs and insights into the future directions of this field of research was performed in detail [10, 27-29, 62].

MicroRNA`s and Pediatric Heart Failure

Noncoding RNAs are RNA molecules that do not code for proteins. Research on dysregulated ncRNAs in human diseases like cancer, neurological disorders, and cardiovascular diseases has been ongoing for over a decade. The incidence is 1.13-1.24 cases per 100000 live births. Micro-RNAs and long noncoding RNAs (lncRNAs) are well-studied types of ncRNAs that play crucial roles in gene expression regulation during cardiac development and disease [11]. These ncRNAs are key regulators in congenital heart diseases, influencing cardiovascular development positively or negatively. A recent review focussed on the role of micro-RNAs and lncRNAs in pediatric cardiovascular diseases, preclinical heart failure models, and cardiac development [11].

CONCLUSION

The investigation of microRNA is a new and very current topic in molecular and cell biology. Working with miRNAs is more challenging than with mRNAs because they are quickly degraded due to their small size and ubiquitous presence of degradation enzymes. Quantifying miRNA therefore requires constant work under cooling conditions and specially prepared, RNase-free equipment. Traditionally, the examination of miRNA expression levels is done by converting RNA into synthetic DNA (cDNA) and then quantifying it using quantitative PCR. Recently, it has also become possible to measure miRNA expression on specialized microarray platforms, a method that is gaining popularity. While this allows for the simultaneous assessment of hundreds of miRNAs, the data processing, as is typical with microarrays, is laborious and often associated with high variability. However, this can often be compensated for by subsequent analysis of the datasets, which ideally also include information on the regulated mRNAs. In recent years, it has been found that miRNAs act as significant regulators of gene translation following gene transcription. This occurs through specific binding to mRNA molecules, which can either hinder, completely prevent, or facilitate their translation into proteins. In mammalian cells, over 800 different miRNAs have been identified so far; in humans, there are currently over 1,800 different miRNA species known to exist in collections, so-called libraries. Comparing invertebrate and vertebrate cells shows that the structure of some of these molecules is highly conserved, indicating an important common evolutionary function in very different species. Experimental and computational studies suggest that each miRNA can regulate several mRNA molecules, and that 20-30% of all human genes are co-regulated by miRNAs. The type and number of miRNA molecules produced in the cell nucleus often show a close correlation with the cell's developmental stage (cell division, differentiation into specific cell types, apoptosis). miRNAs act in a regulatory network with

transcription factors (TFs). Recent studies demonstrate the critical function of miRNAs in early developmental processes of animals, such as neurogenesis, myogenesis, cardiogenesis, and hematopoiesis. miRNAs also play an important role in plants. It has been suggested that miRNAs are crucial for suppressing cellular transformations such as tumor formation, as faulty miRNA molecule formation in cells can enhance these undesirable processes. Deregulation of miRNAs has been observed in various types of tumors and seems to exhibit tumor-specific characteristics. The influence of the tumor suppressor protein p53 on the maturation of various miRNAs that inhibit cell growth also supports this conclusion. The potential role of miRNAs in the pathogenesis, diagnosis, and treatment of epilepsy has also been highlighted. Changes in miRNA levels in patients with temporal lobe epilepsy and animal models have been identified. Functional studies have shown promising results, including the strong antiepileptic effects of suppressing brain-specific miR-134. Changes in miRNA expression have also been observed in other refractory epilepsy types, expanding the understanding of miRNA regulation, delivery methods, and diagnostic biomarker potential. Recent research indicates that certain miRNAs are important for maintaining pluripotency and self-renewal of embryonic stem cells. Therefore, microRNAs could potentially serve as useful molecular tools for manipulating stem cells in the future. For research purposes, cellular microRNA molecules can be inhibited using complementary antagomirs. The presence of certain microRNAs may also be used for diagnosing diseases such as myocarditis. Recent findings suggest that miRNA can be ingested through food and influence processes in the body. Many different studies in childhood concentrate on different pediatric diseases and the role in pathogenesis of microRNA [1-62]. Micro RNA`s seem to play important roles in many different pediatric diseases, of which only few of them were stated in this review, suggesting an important role for the pathogenesis of these diseases in childhood. To date, there are many different report in literature focussing on special kind of microRNAs and their role in pediatric pathogenesis. Further intensive research efforts must be undertaken to closely analyze these different microRNAs and possibly use them as a predictive biomarker in the future.

CONFLICTS OF INTEREST

No conflict of interest

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